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(57) Abstract

The invention relates to a nucleic material, in the isolated or purified state, comprising a nucleotide sequence selected from the group including sequences SEQ ID NO:93, SEQ ID NO:94, their complementary sequences and their equivalent sequences, in particular nucleotide sequences displaying, for any succession of 100 contiguous monomers, at least 50 % and preferably at least 60 % homology with said sequences SEQ ID NO:93, SEQ ID NO:94 and their complementary sequences, excluding HSERV-9 sequence.

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VIRAL MATERIAL AND NUCLEOTIDE FRAGMENTS ASSOCIATED WITH MULTIPLE SCLEROSIS, FOR DIAGNOSTIC, PROPHYLACTIC AND THERAPEUTIC PURPOSES

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) the cause of which remains as yet unknown.

"Multiple sclerosis (MS) is the most common neurological disease of young adults with a prevalence in Europe and North America of between 20 and 200 per 100,000. It is characterized clinically by a relapsing/remitting or chronic progressive course, frequently leading to severe disability. Current knowledge suggests that MS is associated with autoimmunity, that genetic background has an important influence and that "infectious" agent(s) may be involved. Indeed, many viruses have been proposed as possible candidates but as yet, none of them has been shown to play an aetiological role.

Many studies have supported the hypothesis of a viral aetiology of the disease, but none of the known viruses tested has proved to be the causal agent sought: a review of the viruses sought for several years in MS has been compiled by E. Norrby (1) and R.T. Johnson (2).

The discovery of pathogenic retroviruses in man (HTLVs and HIVs) was followed by great interest in their ability to impair the immune system and to provoke central nervous system inflammation and/or degeneration. In the case of HTLV-1, its association with a chronic inflammatory demyelinating disease in man (48) led to extensive investigations to search for an HTLV1-like retrovirus in MS patients. However, despite initial claims, the presence of HTLV-1 or HTLV-like retroviruses was not confirmed.

Recently, a retrovirus different from the known human retroviruses has been isolated in patients suffering from MS (3, 4, and 5).

In 1989, the authors described the production of extracellular virions, associated with reverse transcriptase (RT) activity, by a culture of leptomeningeal cells (LM7) obtained from the cerebrospinal fluid of a patient with MS (3). This was followed by similar findings in monocyte cultures from a series of MS patients (5). Neither viral particles nor viral RT-activity were found in control individuals. Furthermore, the authors were able to transfer the LM7 virus to non-infected leptomeningeal cells *in vitro* (26). The molecular characterization of the "LM7" retrovirus was a prerequisite for further evaluation of its possible role in MS. Considerable difficulties arose from the absence of continuously productive retroviral cultures and from the low levels of expression in the few transient cultures. The strategy described here focused on RNA from extracellular virions, in order to avoid non-specific detection of cellular RNA and of endogenous elements from contaminating human DNA. A specific retroviral sequence associated with virions produced by cell cultures from several MS patients has been identified. The entire sequence of this novel retroviral genome is currently being obtained using RT-PCR on RNA from extracellular virions. The retrovirus previously called "LM7 virus" corresponds to an oncovirus and is now designated MSRV (Multiple Sclerosis-associated RetroVirus).

The authors were also able to show that this retrovirus could be transmitted in vitro, that patients suffering from MS produced antibodies capable of recognizing proteins associated with the infection of leptomeningeal cells by this retrovirus, and that the expression of the latter could be strongly stimulated by the immediate-early genes of some herpesviruses (6).

All these results point to the role in MS of at least one unknown retrovirus or of a virus having reverse transcriptase activity which is detectable according to the method published by H. Perron (3) and qualified as "LM7-like RT" activity. The content of the publication identified by (3) is incorporated in the present description by reference.

Recently, the Applicant's studies have enabled two continuous cell lines infected with natural isolates originating from two different patients suffering from MS to be obtained by a culture method as described in the document WO-A-93/20188, the content of which is incorporated in the present description by reference. These two lines, derived from human choroid plexus cells, designated LM7PC and PLI-2, were deposited with the ECACC on 22nd July 1992 and 8th January 1993, respectively, under numbers 92072201 and 93010817, in accordance with the provisions of the Budapest Treaty. Moreover, the viral isolates possessing LM7-like RT activity were also deposited with the ECACC under the overall designation of "strains". The "strain" or isolate harboured by the PLI-2 line, designated POL-2, was deposited with the ECACC on 22nd July 1992 under No. V92072202. The "strain" or isolate harboured by the LM7PC line, designated MS7PG, was deposited with the ECACC on 8th January 1993 under No. V93010816.

Starting from the cultures and isolates mentioned above, characterized by biological and morphological criteria, the next step was to endeavour to characterize the nucleic acid material associated with the viral particles produced in these cultures.

The portions of the genome which have already been characterized have been used to develop tests for molecular detection of the viral genome and immunoserological tests, using the amino acid sequences encoded by the nucleotide sequences of the viral genome,

in order to detect the immune response directed against epitopes associated with the infection and/or viral expression.

These tools have already enabled an association to be confirmed between MS and the expression of the sequences identified in the patents cited later. However, the viral system discovered by the Applicant is related to a complex retroviral system. In effect, the sequences to be found encapsidated in the extracellular viral particles produced by the different cultures of cells of patients suffering from MS show clearly that there is coencapsidation of retroviral genomes which are related but different from the "wild-type" retroviral genome which produces the infective viral particles. This phenomenon has been observed between replicative retroviruses and endogenous retroviruses belonging to the same family, or even heterologous retroviruses. The notion of endogenous retroviruses is very important in the context of our discovery since, in the case of MSRV-1, it has been observed that endogenous retroviral sequences comprising sequences homologous to the MSRV-1 genome exist in normal human DNA. The existence of endogenous retroviral elements (ERV) related to MSRV-1 by all or part of their genome explains the fact that the expression of the MSRV-1 retrovirus in human cells is able to interact with closely related endogenous sequences. These interactions are to be found in the case of pathogenic and/or infectious endogenous retroviruses (for example some ecotropic strains of the murine leukaemia virus), and in the case of exogenous retroviruses whose nucleotide sequence may be found partially or wholly, in the form of ERVs, in the host animal's genome (e.g. mouse exogenous mammary tumor virus transmitted via the milk). These interactions consist mainly of (i) a trans-activation or coactivation of ERVs by the replicative retrovirus (ii) and "illegitimate" encapsidation of RNAs related to ERVS, or

of ERVs - or even of cellular RNAs - simply possessing compatible encapsidation sequences, in the retroviral particles produced by the expression of the replicative strain, which are sometimes transmissible and sometimes with a pathogenicity of their own, and (iii) more or less substantial recombinations between the coencapsidated genomes, in particular in the phases of reverse transcription, which lead to the formation of hybrid genomes, which are sometimes transmissible and sometimes with a pathogenicity of their own.

Thus, (i) different sequences related to MSRV-1 have been found in the purified viral particles; (ii) molecular analysis of the different regions of the MSRV-1 retroviral genome should be carried out by systematically analyzing the coencapsidated, interfering and/or recombined sequences which are generated by the infection and/or expression of MSRV-1; furthermore, some clones may have defective sequence portions produced by the retroviral replication and template errors and/or errors of transcription of the reverse transcriptase; (iii) the families of sequences related to the same retroviral genomic region provide the means for an overall diagnostic detection which may be optimized by the identification of invariable regions among the clones expressed, and by the identification of reading frames responsible for the production of antigenic and/or pathogenic polypeptides which may be produced only by a portion, or even by just one, of the clones expressed, and, under these conditions, the systematic analysis of the clones expressed in the region of a given gene enables the frequency of variation and/or of recombination of the MSRV-1 genome in this region to be evaluated and the optimal sequences for the applications, in particular diagnostic applications, to be defined; (iv) the pathology caused by a retrovirus such as MSRV-1 may be a direct effect of its expression and of the proteins or peptides produced as a result thereof, but

also an effect of the activation, the encapsidation or the recombination of related or heterologous genomes and of the proteins or peptides produced as a result thereof; thus, these genomes associated with the expression of and/or infection by MSRV-1 are an integral part of the potential pathogenicity of this virus, and hence constitute means of diagnostic detection and special therapeutic targets. Similarly, any agent associated with or cofactor of these interactions responsible for the pathogenesis in question, such as MSRV-2 or the gliotoxic factor which are described in the patent application published under No. FR-2,716,198, may participate in the development of an overall and very effective strategy for the diagnosis, prognosis, therapeutic monitoring and/or integrated therapy of MS in particular, but also of any other disease associated with the same agents.

In this context, a parallel discovery has been made in another autoimmune disease, rheumatoid arthritis (RA), which has been described in the French Patent Application filed under No. 95/02960. This discovery shows that, by applying methodological approaches similar to the ones which were used in the Applicant's work on MS, it was possible to identify a retrovirus expressed in RA which shares the sequences described for MSRV-1 in MS, and also the coexistence of an associated MSRV-2 sequence also described in MS. As regards MSRV-1, the sequences detected in common in MS and RA relate to the pol and gag genes. In the current state of knowledge, it is possible to associate the gag and pol sequences described with the MSRV-1 strains expressed in these two diseases.

The present patent application relates to various results which are additional to those already protected by the following French Patent Applications:

- No. 92/04322 of 03.04.1992, published under No. 2,689,519;

- No. 92/13447 of 03.11.1992, published under No. 2,689,521;
- No. 92/13443 of 03.11.1992, published under No. 2,689,520;
- No. 94/01529 of 04.02.1994, published under No. 2,715,936;
- No. 94/01531 of 04.02.1994, published under No. 2,715,939;
- No. 94/01530 of 04.02.1994, published under No. 2,715,936;
- No. 94/01532 of 04.02.1994, published under No. 2,715,937;
- No. 94/14322 of 24.11.1994, published under No. 2,727,428;
- and No. 94/15810 of 23.12.1994; published under No. 2,728,585.

The present invention relates, in the first place, to a viral material, in the isolated or purified state, which may be recognized or characterized in different ways:

- its genome comprises a nucleotide sequence chosen from the group including the sequences SEQ ID NO:46, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:89, their complementary sequences and their equivalent sequences, in particular nucleotide sequences displaying, for any succession of 100 contiguous monomers, at least 50% and preferably at least 70% homology with the said sequences SEQ ID NO:46, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60 SEQ ID NO:61, SEQ ID NO:89, respectively, and their complementary sequences;
- the region of its genome comprising the env and pol genes and a portion of the gag gene, excluding the subregion having a sequence identical or equivalent to SEQ ID NO:1, codes for any polypeptide displaying, for any

contiguous succession of at least 30 amino acids, at least 50% and preferably at least 70% homology with a peptide sequence encoded by any nucleotide sequence chosen from the group including SEQ ID NO:46, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60 SEQ ID NO:61 SEQ ID NO:89 and their complementary sequences;

- the pol gene comprises a nucleotide sequence partially or totally identical or equivalent to SEQ ID NO:57 or SEQ ID NO:93, excluding SEQ ID NO:1.
- the gag gene comprises a nucleotide sequence partially or totally identical or equivalent to SEQ ID NO:88.

As indicated above, according to the present invention, the viral material as defined above is associated with MS. And as defined by reference to the pol or gag gene of MSRV-1, and more especially to the sequences SEQ ID NOS 51, 56, 57, 59, 60, 61, 88, 89, 93, 169, 170, 171, 172, 176, 177, 178 and 179, this viral material is associated with RA.

The present invention also relates to a nucleic material, in the isolated or purified state, having at least one of the following definitions :

- a nucleic material comprising a nucleotide sequence selected from the group including sequences SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, their complementary sequences and their equivalent sequences, in particular nucleotide sequences displaying, for any succession of 100 contiguous monomers, at least 50% and preferably at least 60% homology with said sequences SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, and their complementary sequences, excluding HSERV-9 (or ERV-9) ; advantageously, the nucleotide sequence of said nucleic material is

selected from the group including sequences SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, their complementary sequences and their equivalent sequences, in particular nucleotide sequences displaying, for any succession of 100 contiguous monomers, at least 70% and preferably at least 80% homology with said sequences SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, and their complementary sequences ;

- a nucleic material, in the isolated or purified state, coding for any polypeptide displaying, for any contiguous succession of at least 30 amino acids, at least 50%, preferably at least 60 %, and most preferably at least 70% homology with a peptide sequence encoded by any nucleotide sequence selected from the group including SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179 and their complementary sequences;

- a nucleic material, in the isolated or purified state, of retroviral type, comprising a nucleotide sequence identical or similar to at least part of the pol gene of an isolated retrovirus associated with multiple sclerosis or rheumatoid arthritis; advantageously, said nucleotide sequence is 80 % similar to said at least part of the gene pol;

- a nucleic material comprising a nucleotide sequence identical or similar to at least part of the pol gen of an isolated virus encoding a reverse transcriptase having a enzymatic site comprised between the amino acid domains LPQG-YXDD, having a phylogenic distance with HSERV-9 of 0.063 ± 0.1, and preferably 0.063 ± 0.05; the phylogenic distances are calculated on the basis of a reference

sequence according to UPGM tree option of the Geneworks™ Software (INTELLIGENETICS) ;
By enzymatic site, we understand the amino acids domain(s) conferring the specific activity of a given enzyme.

The present invention also relates to different nucleotide fragments each comprising a nucleotide sequence chosen from the group including:
(a) all the genomic sequences, partial and total, of the pol gene of the MSRV-1 virus, except for the total sequence of the nucleotide fragment defined by SEQ ID NO:1;
(b) all the genomic sequences, partial and total, of the env gene of MSRV-1;
(c) all the partial genomic sequences of the gag gene of MSRV-1;
(d) all the genomic sequences overlapping the pol gene and the env gene of the MSRV-1 virus, and overlapping the pol gene and the gag gene;
(e) all the sequences, partial and total, of a clone chosen from the group including the clones FBd3 (SEQ ID NO:46), t pol (SEQ ID NO:51), JLBc1 (SEQ ID NO:52), JLBc2 (SEQ ID NO:53) and GM3 (SEQ ID NO:56), FBd13 (SEQ ID NO:58), LB19 (SEQ ID NO:59), LTRGAG12 (SEQ ID NO:60), FP6 (SEQ ID NO:61), G+E+A (SEQ ID NO:89), excluding any nucleotide sequence identical to or lying within the sequence defined by SEQ ID NO:1;
(f) sequences complementary to the said genomic sequences;
(g) sequences equivalent to the said sequences (a) to (e), in particular nucleotide sequences displaying, for any succession of 100 contiguous monomers, at least 50% and preferably at least 70% homology with the said sequences (a) to (d),
provided that this nucleotide fragment does not comprise or consist of the sequence ERV-9 as described in LA MANTIA et al. (18).

The term genomic sequences, partial or total, includes all sequences associated by coencapsidation or by coexpression, or recombined sequences.

Preferably, such a fragment comprises:

- either a nucleotide sequence identical to a partial or total genomic sequence of the pol gene of the MSRV-1 virus, except for the total sequence of the nucleotide fragment defined by SEQ ID NO:1, or identical to any sequence equivalent to the said partial or total genomic sequence, in particular one which is homologous to the latter;
- or a nucleotide sequence identical to a partial or total genomic sequence of the env gene of the MSRV-1 virus, or identical to any sequence complementary to the said nucleotide sequence, or identical to any sequence equivalent to the said nucleotide sequence, in particular one which is homologous to the latter.

In particular, the invention relates to a nucleotide fragment comprising a coding nucleotide sequence which is partially or totally identical to a nucleotide sequence chosen from the group including:

- the nucleotide sequence defined by SEQ ID NO:40, SEQ ID NO:62 or SEQ ID NO:89;
- sequences complementary to SEQ ID NO:40, SEQ ID NO:62 or SEQ ID NO:89;
- sequences equivalent, and in particular homologous to SEQ ID NO:40, SEQ ID NO:62 or SEQ ID NO:89;
- sequences coding for all or part of the peptide sequence defined by SEQ ID NO:39, SEQ ID NO:63 or SEQ ID NO:90;
- sequences coding for all or part of a peptide sequence equivalent, in particular homologous to SEQ ID NO:39, SEQ ID NO:63 or SEQ ID NO:90, which is capable of being recognized by sera of patients infected with the MSRV-1 virus, or in whom the MSRV-1 virus has been reactivated.

The invention also relates to a nucleotide fragment (called fragment I) having at least one of the following definitions :

- a nucleotide fragment comprising a nucleotide sequence selected from the group including SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, their complementary sequences and their equivalent sequences, in particular nucleotide sequences displaying, for any succession of 100 contiguous monomers, at least 50% and preferably at least 60% homology with said sequences and their complementary sequences, said group excluding SEQ ID NO:1, said nucleotide fragment not comprising nor consisting of the sequence HSERV-9 (or ERV-9); preferably the nucleotide sequence of said fragment is selected from the group including SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179, their complementary sequences and their equivalent sequences, in particular nucleotide sequences displaying, for any succession of 100 contiguous monomers, at least 70% and preferably at least 80% homology with said sequences and their complementary sequences;
- a nucleotide fragment comprising a coding nucleotide sequence which is partially or totally identical to a nucleotide sequence selected from the group including :

SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179 ; their complementary sequences ; their equivalent sequences, in particular homologous to SEQ ID NO:93, SEQ ID NO:94, SEQ ID NO:169, SEQ ID NO:170, SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:179;

sequences encoding all or parts of the peptide sequence defined by SEQ ID NO:95, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:175, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182;

sequences encoding all or parts of a peptide sequence equivalent, in particular homologous to SEQ ID NO:95, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:175, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, which is capable of being recognized by sera of patients infected with the MSRV-1 virus, or in whom the MSRV-1 virus has been reactivated.

The invention also relates to any nucleic acid probe for the detection of virus associated with MS and/or rheumatoid arthritis (RA), which is capable of hybridizing specifically with any fragment such as is defined above, belonging or lying within the genome of the said pathogenic agent. It relates, in addition, to any nucleic acid probe for detection of a pathogenic and/or infective agent associated with RA, which is capable of hybridizing specifically with any fragment as defined above by reference to the pol and gag genes, and especially with respect to the sequences SEQ ID NOS 40, 51, 56, 59, 60, 61, 62, 89 and SEQ ID NOS 39, 63 and 90.

The invention also relates to a primer for the amplification by polymerization of an RNA or a DNA of a viral material, associated with MS and/or RA, comprising a nucleotide sequence identical or equivalent to at least one portion of the nucleotide sequence of any fragment such as is defined above, in particular a nucleotide sequence displaying, for any succession of at least 10 contiguous monomers, preferably 15 contiguous monomers, more preferably 18 contiguous monomers and even most preferably 20 contiguous monomers, at least 70% homology with at least the said portion of the said fragment. Preferably, the nucleotide sequence of such a primer is identical to any one of the sequences selected from the

group including SEQ ID NO:47 to SEQ ID NO:50, SEQ ID NO:55, SEQ ID NO:64, SEQ ID NO:86, SEQ ID NO:99 to SEQ ID NO:111, SEQ ID NO:183, SEQ ID NO:184, SEQ ID NO:185, SEQ ID NO:186.

Generally speaking the invention also encompasses any RNA or DNA, and in particular replication vector, comprising a genomic fragment of the viral material such as is defined above, or a nucleotide fragment such as is defined above.

The invention also relates to the different peptides encoded by any open reading frame belonging to a nucleotide fragment such as is defined above, in particular any polypeptide, for example any oligopeptide forming or comprising an antigenic determinant recognized by sera of patients infected with the MSRV-1 virus and/or in whom the MSRV-1 virus has been reactivated. Preferably, this polypeptide is antigenic, and is encoded by the open reading frame beginning, in the 5'-3' direction, at nucleotide 181 and ending at nucleotide 330 of SEQ ID NO:1.

The invention also encompasses the following polypeptides :

a)

- a polypeptide encoded by any open reading frame belonging to a nucleotide fragment, fragment I, as defined above ;

- a polypeptide, characterized in that the open reading frame encoding it, is comprised, in the 5'-3' direction, between nucleotide 18 and nucleotide 2304 of SEQ ID NO:93;

- a polypeptide, having a peptide sequence comprising a sequence partially or totally identical to SEQ ID NO:95;

b)

- a polypeptide, recombinant or synthetic, having a peptide sequence which comprises a sequence identical or equivalent to SEQ ID NO:96; in particular said polypeptide

exhibits an enzymatic activity consisting of proteolytic activity;

- a polypeptide, recombinant or synthetic, characterized in that the open reading frame encoding it begins, in the 5'-3' direction, at nucleotide 18 and ends at nucleotide 340 of SEQ ID NO:93;

- a polypeptide having an inhibitory activity on the proteolytic activity of a polypeptide as defined according to b);

c)

- a polypeptide, recombinant or synthetic, having a peptide sequence which comprises a sequence identical or equivalent to SEQ ID NO:97; in particular said polypeptide exhibits a reverse transcriptase activity;

- a polypeptide having a peptide sequence which comprises a sequence identical or equivalent to SEQ ID NO:98; in particular said polypeptide exhibits a ribonuclease activity;

- a polypeptide, recombinant or synthetic, characterized in that the open reading frame encoding it begins, in the 5'-3' direction, at nucleotide 341 and ends at nucleotide 2304 of SEQ ID NO:93;

- a polypeptide, recombinant or synthetic, characterized in that the open reading frame encoding it begins, in the 5'-3' direction, at nucleotide 1858 and ends at nucleotide 2304 of SEQ ID NO:93.

- a polypeptide having an inhibitory activity on the reverse transcriptase activity of a polypeptide as defined according to c) or on the ribonuclease H activity of a polypeptide as defined according to c).

In particular, the invention relates to an antigenic polypeptide recognized by the sera of patients infected with the MSRV-1 virus, and/or in whom the MSRV-1 virus has been reactivated, whose peptide sequence is partially or totally identical or is equivalent to the sequence defined by SEQ ID NO:39, SEQ ID NO:63,

SEQ ID NO:87, SEQ ID NO:95, SEQ ID NO:96, SEQ ID NO:97, SEQ ID NO:98, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:175, SEQ ID NO:180, SEQ ID NO:181 and SEQ ID NO:182; such a sequence is identical, for example, to any sequence selected from the group including the sequences SEQ ID NO:41 to SEQ ID NO:44, SEQ ID NO:63 and SEQ ID NO:87.

The present invention also proposes mono- or polyclonal antibodies directed against the MSRV-1 virus, which are obtained by the immunological reaction of a human or animal body or cells to an immunogenic agent consisting of an antigenic polypeptide such as is defined above.

The invention next relates to:

- reagents for detection of the MSRV- virus, or of an exposure to the latter, comprising, at least one reactive substance selected from the group consisting of a probe of the present invention, a polypeptide, in particular an antigenic peptide, such as is defined above, or an anti-ligand, in particular an antibody to the said polypeptide;
- all diagnostic, prophylactic or therapeutic compositions comprising one or more peptides, in particular antigenic peptides, such as are defined above, or one or more anti-ligands, in particular antibodies to the peptides, discussed above; such a composition is preferably, and by way of example, a vaccine composition.

The invention also relates to any diagnostic, prophylactic or therapeutic composition, in particular for inhibiting the expression of at least one virus associated with MS or RA, and/or the enzymatic activities of the proteins of said virus, comprising a nucleotide fragment such as is defined above or a polynucleotide, in particular oligonucleotide, whose sequence is partially identical to that of the said fragment, except for that of the fragment having the nucleotide sequence SEQ ID NO:1. Likewise, it relates to any diagnostic, prophylactic or

therapeutic composition, in particular for inhibiting the expression of at least one pathogenic and/or infective agent associated with RA, comprising a nucleotide fragment such as is defined above by reference to the pol and gag genes, and especially with respect to the sequences SEQ ID NOS 40, 51, 56, 59, 60, 61, 62 and 89.

According to the invention, these same fragments or polynucleotides, in particular oligonucleotides, may participate in all suitable compositions for detecting, according to any suitable process or method, a pathological and/or infective agent associated with MS and with RA, respectively, in a biological sample. In such a process, an RNA and/or a DNA presumed to belong or originating from the said pathological and/or infective agent, and/or their complementary RNA and/or DNA, is/are brought into contact with such a composition.

The present invention also relates to any process for detecting the presence or exposure to such a pathological and/or infective agent, in a biological sample, by bringing this sample into contact with a peptide, in particular an antigenic peptide such as is defined above, or an anti-ligand, in particular an antibody to this peptide, such as is defined above.

In practice, and for example, a device for detection of the MSRV-1 virus comprises a reagent such as is defined above, supported by a solid support which is immunologically compatible with the reagent, and a means for bringing the biological sample, for example a sample of blood or of cerebrospinal fluid, likely to contain anti-MSRV-1 antibodies, into contact with this reagent under conditions permitting a possible immunological reaction, the foregoing items being accompanied by means for detecting the immune complex formed with this reagent.

Lastly, the invention also relates to the detection of anti-MSRV-1 antibodies in a biological sample, for example a sample of blood or of cerebrospinal fluid,

according to which this sample is brought into contact with a reagent such as is defined above, consisting of an antibody, under conditions permitting their possible immunological reaction, and the presence of the immune complex thereby formed with the reagent is then detected.

Before describing the invention in detail, different terms used in the description and the claims are now defined:

- strain or isolate is understood to mean any infective and/or pathogenic biological fraction containing, for example, viruses and/or bacteria and/or parasites, generating pathogenic and/or antigenic power, harboured by a culture or a living host; as an example, a viral strain according to the above definition can contain a coinfective agent, for example a pathogenic protist,

- the term "MSRV" used in the present description denotes any pathogenic and/or infective agent associated with MS, in particular a viral species, the attenuated strains of the said viral species or the defective-interfering particles or particles containing coencapsidated genomes, or alternatively genomes recombined with a portion of the MSRV-1 genome, derived from this species. Viruses, and especially viruses containing RNA, are known to have a variability resulting, in particular, from relatively high rates of spontaneous mutation (7), which will be borne in mind below for defining the notion of equivalence,

- human virus is understood to mean a virus capable of infecting, or of being harboured by human beings,

- in view of all the natural or induced variations and/or recombination which may be encountered when implementing the present invention, the subjects of the latter, defined above and in the claims, have been expressed including the equivalents or derivatives of the different biological materials defined below, in

particular of the homologous nucleotide or peptide sequences,

- the variant of a virus or of a pathogenic and/or infective agent according to the invention comprises at least one antigen recognized by at least one antibody directed against at least one corresponding antigen of the said virus and/or said pathogenic and/or infective agent, and/or a genome any part of which is detected by at least one hybridization probe and/or at least one nucleotide amplification primer specific for the said virus and/or pathogenic and/or infective agent, such as, for example, for the MSRV-1 virus, the primers and probes having a nucleotide sequence chosen from SEQ ID NO:20 to SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:16 to SEQ ID NO:19, SEQ ID NO:31 to SEQ ID NO:33, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:45 and their complementary sequences, under particular hybridization conditions well known to a person skilled in the art,

- according to the invention, a nucleotide fragment or an oligonucleotide or polynucleotide is an arrangement of monomers, or a biopolymer, characterized by the informational sequence of the natural nucleic acids, which is capable of hybridizing with any other nucleotide fragment under predetermined conditions, it being possible for the arrangement to contain monomers of different chemical structures and to be obtained from a molecule of natural nucleic acid and/or by genetic recombination and/or by chemical synthesis; a nucleotide fragment may be identical to a genomic fragment of the MSRV-1 virus discussed in the present invention, in particular a gene of this virus, for example pol or env in the case of the said virus,

- thus, a monomer can be a natural nucleotide of nucleic acid whose constituent elements are a sugar, a phosphate group and a nitrogenous base; in RNA the sugar

is ribose, in DNA the sugar is 2-deoxyribose; depending on whether the nucleic acid is DNA or RNA, the nitrogenous base is chosen from adenine, guanine, uracil, cytosine and thymine; or the nucleotide can be modified in at least one of the three constituent elements; as an example, the modification can occur in the bases, generating modified bases such as inosine, 5-methyldeoxycytidine, deoxyuridine, 5-(dimethylamino)deoxyuridine, 2,6-diaminopurine, 5-bromodeoxyuridine and any other modified base promoting hybridization; in the sugar, the modification can consist of the replacement of at least one deoxyribose by a polyamide (8), and in the phosphate group, the modification can consist of its replacement by esters chosen, in particular, from diphosphate, alkyl- and arylphosphonate and phosphorothioate esters,

- "informational sequence" is understood to mean any ordered succession of monomers whose chemical nature and order in a reference direction constitute or otherwise an item of functional information of the same quality as that of the natural nucleic acids,

- hybridization is understood to mean the process during which, under suitable working conditions, two nucleotide fragments having sufficiently complementary sequences pair to form a complex structure, in particular double or triple, preferably in the form of a helix,

- a probe comprises a nucleotide fragment synthesized chemically or obtained by digestion or enzymatic cleavage of a longer nucleotide fragment, comprising at least six monomers, advantageously from 10 to 1000 monomers, preferably 10 to 30 monomers and more preferably 18 to 30, and possessing a specificity of hybridization under particular conditions; preferably, a probe possessing fewer than 10 monomers, but preferably fewer than 15 monomers is not used alone, but is used in the presence of other probes of equally short size or otherwise; under certain special conditions, it may be useful to use probes

of size greater than 100 monomers; a probe may be used, in particular, for diagnostic purposes, such molecules being, for example, capture and/or detection probes,

- the capture probe may be immobilized on a solid support by any suitable means, that is to say directly or indirectly, for example by covalent bonding or passive adsorption,

- the detection probe may be labelled by means of a label chosen, in particular, from radioactive isotopes, enzymes chosen, in particular, from peroxidase and alkaline phosphatase and those capable of hydrolysing a chromogenic, fluorogenic or luminescent substrate, chromophoric chemical compounds, chromogenic, fluorogenic or luminescent compounds, nucleotide base analogues and biotin,

- the probes used for diagnostic purposes of the invention may be employed in all known hybridization techniques, and in particular the techniques termed "DOT-BLOT" (9), "SOUTHERN BLOT" (10), "NORTHERN BLOT", which is a technique identical to the "SOUTHERN BLOT" technique but which uses RNA as target, and the SANDWICH technique (11); advantageously, the SANDWICH technique is used in the present invention, comprising a specific capture probe and/or a specific detection probe, on the understanding that the capture probe and the detection probe must possess an at least partially different nucleotide sequence,

- any probe according to the present invention can hybridize in vivo or in vitro with RNA and/or with DNA in order to block the phenomena of replication, in particular translation and/or transcription, and/or to degrade the said DNA and/or RNA,

- a primer is a probe comprising at least six monomers, and advantageously from 10 to 30 monomers, and preferably from 18 to 25 monomers, possessing a specificity of hybridization under particular conditions

for the initiation of an enzymatic polymerization, for example in an amplification technique such as PCR (polymerase chain reaction), in an elongation process such as sequencing, in a method of reverse transcription or the like,

- two nucleotide or peptide sequences are termed equivalent or derived with respect to one another, or with respect to a reference sequence, if functionally the corresponding biopolymers can perform substantially the same role, without being identical, as regards the application or use in question, or in the technique in which they participate; two sequences are, in particular, equivalent if they are obtained as a result of natural variability, in particular spontaneous mutation of the species from which they have been identified, or induced variability, as are two homologous sequences, homology being defined below,

- "variability" is understood to mean any spontaneous or induced modification of a sequence, in particular by substitution and/or insertion and/or deletion of nucleotides and/or of nucleotide fragments, and/or extension and/or shortening of the sequence at one or both ends; an unnatural variability can result from the genetic engineering techniques used, for example the choice of synthesis primers, degenerate or otherwise, selected for amplifying a nucleic acid; this variability can manifest itself in modifications of any starting sequence, considered as reference, and capable of being expressed by a degree of homology relative to the said reference sequence,

- homology characterizes the degree of identity of two nucleotide or peptide fragments compared; it is measured by the percentage identity which is determined, in particular, by direct comparison of nucleotide or peptide sequences, relative to reference nucleotide or peptide sequences,

- this percentage identity has been specifically determined for the nucleotide fragments, clones in particular, dealt with in the present invention, which are homologous to the fragments identified, for the MSRV-1 virus, by SEQ ID NO:1 to NO:9, SEQ ID NO:46, SEQ ID NO:51 to SEQ ID NO:53, SEQ ID NO:40, SEQ ID NO:56, SEQ ID NO:57 and SEQ ID NO:93, as well as for the probes and primers homologous to the probes and primers identified by SEQ ID NO:20 to SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:16 to SEQ ID NO:19, SEQ ID NO:31 to SEQ ID NO:33, SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:55, SEQ ID NO:40, SEQ ID NO:56, SEQ ID NO:57 and SEQ ID NO:99 to SEQ ID NO:111; as an example, the smallest percentage identity observed between the different general consensus sequences of nucleic acids obtained from fragments of MSRV-1 viral RNA, originating from the LM7PC and PLI-2 lines according to a protocol detailed later, is 67% in the region described in Figure 1,

- any nucleotide fragment is termed equivalent or derived from a reference fragment if it possesses a nucleotide sequence equivalent to the sequence of the reference fragment; according to the above definition, the following in particular are equivalent to a reference nucleotide fragment:

a) any fragment capable of hybridizing at least partially with the complement of the reference fragment,

b) any fragment whose alignment with the reference fragment results in the demonstration of a larger number of identical contiguous bases than with any other fragment originating from another taxonomic group,

c) any fragment resulting, or capable of resulting, from the natural variability of the species from which it is obtained,

d) any fragment capable of resulting from the genetic engineering techniques applied to the reference fragment,

e) any fragment containing at least eight contiguous nucleotides encoding a peptide which is homologous or identical to the peptide encoded by the reference fragment,

f) any fragment which is different from the reference fragment by insertion, deletion or substitution of at least one monomer, or extension or shortening at one or both of its ends; for example, any fragment corresponding to the reference fragment flanked at one or both of its ends by a nucleotide sequence not coding for a polypeptide,

- polypeptide is understood to mean, in particular, any peptide of at least two amino acids, in particular an oligopeptide, or protein, and for example an enzyme, extracted, separated or substantially isolated or synthesized through human intervention, in particular those obtained by chemical synthesis or by expression in a recombinant organism,

- polypeptide partially encoded by a nucleotide fragment is understood to mean a polypeptide possessing at least three amino acids encoded by at least nine contiguous monomers lying within the said nucleotide fragment,

- an amino acid is termed analogous to another amino acid when their respective physicochemical properties, such as polarity, hydrophobicity and/or basicity and/or acidity and/or neutrality are substantially the same; thus, a leucine is analogous to an isoleucine.

- any polypeptide is termed equivalent or derived from a reference polypeptide if the polypeptides compared have substantially the same properties, and in particular the same antigenic, immunological, enzymological and/or molecular recognition properties; the following in particular are equivalent to a reference polypeptide:

a) any polypeptide possessing a sequence in which at least one amino acid has been replaced by an analogous amino acid,

b) any polypeptide having an equivalent peptide sequence, obtained by natural or induced variation of the said reference polypeptide and/or of the nucleotide fragment coding for the said polypeptide,

c) a mimotope of the said reference polypeptide,

d) any polypeptide in whose sequence one or more amino acids of the L series are replaced by an amino acid of the D series, and vice versa,

e) any polypeptide into whose sequence a modification of the side chains of the amino acids has been introduced, such as, for example, an acetylation of the amine functions, a carboxylation of the thiol functions, an esterification of the carboxyl functions,

f) any polypeptide in whose sequence one or more peptide bonds have been modified, such as, for example, carba, retro, inverso, retro-inverso, reduced and methylenoxy bonds,

(g) any polypeptide at least one antigen of which is recognized by an antibody directed against a reference polypeptide,

- the percentage identity characterizing the homology of two peptide fragments compared is, according to the present invention, at least 50% and preferably at least 70%.

In view of the fact that a virus possessing reverse transcriptase enzymatic activity may be genetically characterized equally well in RNA and in DNA form, both the viral DNA and RNA will be referred to for characterizing the sequences relating to a virus possessing such reverse transcriptase activity, termed MSRV-1 according to the present description.

The expressions of order used in the present description and the claims, such as "first nucleotide

sequence", are not adopted so as to express a particular order, but so as to define the invention more clearly.

Detection of a substance or agent is understood below to mean both an identification and a quantification, or a separation or isolation, of the said substance or said agent.

A better understanding of the invention will be gained on reading the detailed description which follows, prepared with reference to the attached figures, in which:

- Figure 1 shows general consensus sequences of nucleic acids of the MSRV-1B clones amplified by the PCR technique in the "pol" region defined by Shih (12), from viral DNA originating from the LM7PC and PLI-2 lines, and identified under the references SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6, and the common consensus with amplification primers bearing the reference SEQ ID NO:7;

- Figure 2 gives the definition of a functional reading frame for each MSRV-1B/"PCR pol" type family, the said families A to D being defined, respectively, by the nucleotide sequences SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6 described in Figure 1;

- Figure 3 gives an example of consensus of the MSRV-2B sequences, identified by SEQ ID NO:11;

- Figure 4 is a representation of the reverse transcriptase (RT) activity in dpm (disintegrations per minute) in the sucrose fractions taken from a purification gradient of the virions produced by the B lymphocytes in culture from a patient suffering from MS;

- Figure 5 gives, under the same experimental conditions as in Figure 4, the assay of the reverse transcriptase activity in the culture of a B lymphocyte line obtained from a control free from MS;

- Figure 6 shows the nucleotide sequence of the clone PSJ17 (SEQ ID NO:9);

- Figure 7 shows the nucleotide sequence SEQ ID NO:8 of the clone designated M003-P004;

- Figure 8 shows the nucleotide sequence SEQ ID NO:2 of the clone F11-1; the portion located between the two arrows in the region of the primer corresponds to a variability imposed by the choice of primer which was used for the cloning of F11-1; in this same figure, the translation into amino acids is shown;
- Figure 9 shows the nucleotide sequence SEQ ID NO:1, and a possible functional reading frame of SEQ ID NO:1 in terms of amino acids; on this sequence, the consensus sequences of the pol gene are underlined;
- Figures 10 and 11 give the results of a PCR, in the form of a photograph under ultraviolet light of an ethidium bromide-impregnated agarose gel, of the amplification products obtained from the primers identified by SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18 and SEQ ID NO:19;
- Figure 12 gives a representation in matrix form of the homology between SEQ ID NO:1 of MSRV-1 and that of an endogenous retrovirus designated HSERV9; this homology of at least 65% is demonstrated by a continuous line, the absence of a line meaning a homology of less than 65%;
- Figure 13 shows the nucleotide sequence SEQ ID NO:46 of the clone FBd3;
- Figure 14 shows the sequence homology between the clone FBd3 and the HSERV-9 retrovirus;
- Figure 15 shows the nucleotide sequence SEQ ID NO:51 of the clone t pol;
- Figures 16 and 17 show, respectively, the nucleotide sequences SEQ ID NO:52 and SEQ ID NO:53 of the clones JLBc1 and JLBc2, respectively;
- Figure 18 shows the sequence homology between the clone JLBc1 and the clone FBd3;
- and Figure 19 the sequence homology between the clone JLBc2 and the clone FBd3;
- Figure 20 shows the sequence homology between the clones JLBc1 and JLBc2;

- Figures 21 and 22 show the sequence homology between the HSERV-9 retrovirus and the clones JLBc1 and JLBc2, respectively;

- Figure 23 shows the nucleotide sequence SEQ ID NO:56 of the clone GM3;

- Figure 24 shows the sequence homology between the HSERV-9 retrovirus and the clone GM3;

- Figure 25 shows the localization of the different clones studied, relative to the genome of the known retrovirus ERV9;

- Figure 26 shows the position of the clones F11-1, M003-P004, MSRV-1B and PSJ17 in the region hereinafter designated MSRV-1 pol*;

- Figure 27, split into three successive Figures 27a-27c, shows a possible reading frame covering the whole of the pol gene;

- Figure 28 shows, according to SEQ ID NO:40, the nucleotide sequence coding for the peptide fragment POL2B, having the amino acid sequence identified by SEQ ID NO:39;

- Figure 29 shows the OD values (ELISA tests) at 492 nm obtained for 29 sera of MS patients and 32 sera of healthy controls tested with an anti-IgG antibody;

- Figure 30 shows the OD values (ELISA tests) at 492 nm obtained for 36 sera of MS patients and 42 sera of healthy controls tested with an anti-IgM antibody;

- Figures 31 to 33 show the results obtained (relative intensity of the spots) for 43 overlapping octapeptides covering the amino acid sequence 61-110, according to the Spotscan technique, respectively with a pool of MS sera, with a pool of control sera and with the pool of MS sera after deduction of a background corresponding to the maximum signal detected on at least one octapeptide with the control serum (intensity = 1), on the understanding that these sera were diluted to 1/50. The

bar at the far right-hand end represents a graphic scale standard unrelated to the serological test;

- Figure 34 shows the SEQ ID NO:41 and SEQ ID NO:42 of two polypeptides comprising immunodominant regions, while SEQ ID NO:43 and 44 represent immunoreactive polypeptides specific to MS;

- Figure 35 shows the nucleotide sequence SEQ ID NO:59 of the clone LB19 and three potential reading frames of SEQ ID NO:59 in terms of amino acids;

- Figure 36 shows the nucleotide sequence SEQ ID NO:88 (GAG*) and a potential reading frame of SEQ ID NO:88 in terms of amino acids;

- Figure 37 shows the sequence homology between the clone FBd13 and the HSERV-9 retrovirus; according to this representation, the continuous line means a percentage homology greater than or equal to 70% and the absence of a line means a smaller percentage homology;

- Figure 38 shows the nucleotide sequence SEQ ID NO:61 of the clone FP6 and three potential reading frames of SEQ ID NO:61 in terms of amino acids;

- Figure 39 shows the nucleotide sequence SEQ ID NO:89 of the clone G+E+A and three potential reading frames of SEQ ID NO:89 in terms of amino acids;

- Figure 40 shows a reading frame found in the region E and coding for an MSRV-1 retroviral protease identified by SEQ ID NO:90;

- Figure 41 shows the response of each serum of patients suffering from MS, indicated by the symbol (+), and of healthy patients, symbolised by (-), tested with an anti-IgG antibody, expressed as net optical density at 492 nm;

- Figure 42 shows the response of each serum of patients suffering from MS, indicated by the symbols (+) and (QS), and of healthy patients (-), tested with an anti-IgM antibody, expressed as net optical density at 492 nm;

- Figure 43 shows the RT-activity profile in sucrose density gradients of pellets from B-cell lines supernatants; Control B-cell line ■ was obtained from the relative of a patient with mitochondriopathy. MS B-Cell line □ was obtained from a patient with definite MS;

- Figure 44 shows the nucleotide and amino acid alignment of the conserved *pol* regions of viruses detected in the study (cf Example 18) by the "Pan-retrovirus" PCR. "Deletions" are represented by dashes and standard single-letter abbreviations are used to designate amino acids and nucleotides (i = inosine). The most highly conserved VLPQG and YXDD regions are shown as separate blocks in bold type at the end of each sequence. Amino acids which are present in all or in all but one of the sequences are underlined. PCR primers (modified from (12)) PAN-UO and PAN-UI are orientated 5' to 3' (sense) whereas primer PAN-DI is 3' to 5' (antisense). Degeneracies are shown above (PAN-UO & PAN-DI) or below (PAN-UI) the PCR primer sequences. "I" denotes the nine base 5' extension *cttggatcc*, "-I" denotes the nine base 5' extension *ctcaagctt*. The capture and detector probes DpV1 and CpV1b used in the ELOSA assay are shown below a representative MSRV-*cpol* sequence. At three positions below the translated MSRV-*cpol* sequence alternative amino acids (representing "non-silent" nucleic acid variations) are shown in italics - *K* and *Y* substitutions were only observed in PLI-1 derived clones whereas *R* and *W* were encoded by a significant proportion of the clones irrespective of derivation. Note that DpV1 is peroxidase labelled and that CpV1b may be biotinylated at the 5' end if streptavidin coated plates are used. The name of each sequence is indicated at the left of the figure.

HTLV1: Human Leukaemia Virus type 1; HIV1: Human Immunodeficiency Virus type 1; MoMLV: Moloney-Murine Leukaemia Virus; MPMV: Mason-Pfizer Monkey Virus. ERV9:

Endogenous Retrovirus 9. MSRV-cpol: Multiple Sclerosis associated RetroVirus conserved pol region.

- Figure 45 shows a phylogenic tree which is based on the conserved amino acid region encoded by the *pol* gene of MSRV and of representative endogenous and exogenous retroviruses and DNA viruses with reverse transcriptase. It was generated by the U.P.G.M.A. tree program of Geneworks® software.

HSRV: Human Spumaretrovirus. EIAV: Equine Infectious Aenemia Virus. BLV: Bovine Leukaemia Virus. HIV1, HIV2: Human Immunodeficiency Viruses type 1 and 2. HTLV1 and HTLV2: Human Leukaemia Viruses type 1 and 2. F-MuLV: Friend-Murine Leukaemia Virus. MoMLV: Moloney-Murine Leukaemia Virus. BAEV: Baboon Endogenous Virus. GaLV/ Gibbon Ape Leukaemia Virus. HUMER41: Human Endogenous Retroviral sequence, clone 41. IAP: Intracisternal A-type Particle. MPMV: Mason-Pfizer Monkey Virus. HERVK10: Human Endogenous Retrovirus K10. MMTV: Mouse Mammary tumour Virus. HSERV9 (ERV9 database sequence): Human sequence of Endogenous Retrovirus 9. MSRV: Multiple Sclerosis associated RetroVirus. SIV: Simian Immunodeficiency Virus; RTLV-H: Reverse Transcriptase-Like Viral sequence H; SFV: Simian Foamy Virus; VISNA: Visna retrovirus; SIV1: Simian Immunodeficiency Virus type 1; SRV-2: Simian Retrovirus type 2; SMRV-H: Squirrel Monkey Retrovirus H.

- Figure 46 shows the MSRV sequence in the Protease and Reverse-Transcriptase regions of the pol gene.

The aminoacid translation is aligned under the corresponding nucleotide sequence. The region corresponding to the Protease ORF cloned in a recombinant vector and expressed in *E. coli*, is boxed. The regions corresponding to the A and B fragments amplified on plasma samples from MS patients are indicated by brackets.The Reverse-Transcriptase (RT) and RNase H (RNH) region is boxed with dotted line. The highly conserved aminoacids

and/or active sites of enzyme activities of both PRT and RT (including RNH) are shown underlined.

- Figure 47A illustrates the pecific detection of MSRV-pol RNA sequence by RT-PCR in the sucrose density fraction associated with RT-activity and in MS plasma ; Figure 47B shows the RT-activity profile on a sucrose density gradient obtained with extracellular virion pelleted from an MS choroid-plexus culture. The photograph below shows an agarose gel loaded with PCR products amplified from round 1 (ST1.1) RT-PCR products with the ST1.2 primer set. From left to right: water control 1 from RT-PCR step with ST1.1 set; water control 2 amplified from water control 1 with ST1.2 nested primers; Molecular weight markers; Fraction n°1 to 10 corresponding to the RT-activity profile shown above; Plasma samples C1 and C2 from healthy blood donors. Plasma samples MS1 and MS2 from two MS patients.

- Figure 48 shows an example of a variant and/or recombined sequence in the region of the pol gene defined by homology with the overlapping regions described in Figure 25, as GM3, MSRV-1 pol*, t pol and FBd3.

- Figure 49 shows the nucleotide (Figure 49A) and amino acid (Figure 49B) alignments of the *pol* region between clones 1, 5 and 8 of the same patient (Experiment 46-7).

- Figure 50 shows the nucleotide (Figure 50A) and amino acid (Figure 50B) alignments of the *pol* region between clones 41, 43 and 42 of the same patient (Experiment 68-1).

- Figure 51 shows the nucleotide (Figure 51A) and amino acid (Figure 51B) alignments of the *pol* region between the consensus sequence (SEQ ID NO: 176) of clones 1, 5 and 8 of the same patient (Experiment 46-7) and SEQ ID NO:1, and between their corresponding peptide sequences.

- Figure 52 shows the nucleotide (Figure 52A) and amino acid (Figure 52B) alignments of the *pol* region between the consensus sequence (SEQ ID NO: 169) of clones 41, 43 and 42 of the same patient (Experiment 68-1) and SEQ ID NO:1, and between their corresponding peptide sequences.

- Figure 53 shows the nucleotide (Figure 53A) and amino acid (Figure 53B) alignments of the *pol* region between the consensus sequence (SEQ ID NO: 176) of clones 1, 5 and 8 of the same patient (Experiment 46-7) and the consensus sequence (SEQ ID NO: 169) of clones 41, 43 and 42 of the same patient (Experiment 68-1).

Table 5 (at the end of the description) shows the sequences obtained by RT-PCR with degenerate pol primers on sucrose density gradient fractions containing the peak of RT-activity or its negative control (cf Example 18) ; and

Table 6 (at the end of the description) shows the clinical data and results of MSRV-cpol detection by "Pan-retro" PCR with specific ELOSA assay, on CSF from MS and control patients (cf Example 18).

EXAMPLE 1: OBTAINING CLONES DESIGNATED MSRV-1B AND MSRV-2B, DEFINING, RESPECTIVELY, A RETROVIRUS MSRV-1 AND A COINFECTIVE AGENT MSRV2, BY "NESTED" PCR AMPLIFICATION OF THE CONSERVED POL REGIONS OF RETROVIRUSES ON VIRION PREPARATIONS ORIGINATING FROM THE LM7PC AND PLI-2 LINES

A PCR technique derived from the technique published by Shih (12) was used. This technique enables all trace of contaminant DNA to be removed by treating all the components of the reaction medium with DNase. It concomitantly makes it possible, by the use of different but overlapping primers in two successive series of PCR amplification cycles, to increase the chances of amplifying a cDNA synthesized from an amount of RNA which is

small at the outset and further reduced in the sample by the spurious action of the DNAse on the RNA. In effect, the DNase is used under conditions of activity in excess which enable all trace of contaminant DNA to be removed before inactivation of this enzyme remaining in the sample by heating to 85°C for 10 minutes. This variant of the PCR technique described by Shih (12) was used on a cDNA synthesized from the nucleic acids of fractions of infective particles purified on a sucrose gradient according to the technique described by H. Perron (13) from the "POL-2" isolate (ECACC No. V92072202) produced by the PLI-2 line (ECACC No. 92072201) on the one hand, and from the MS7PG isolate (ECACC No. V93010816) produced by the LM7PC line (ECACC No. 93010817) on the other hand. These cultures were obtained according to the methods which formed the subject of the patent applications published under Nos WO 93/20188 and WO 93/20189.

After cloning the products amplified by this technique with the TA Cloning Kit® and analysis of the sequence using an Applied Biosystems model 373A Automatic Sequencer, the sequences were analysed using the Geneworks® software on the latest available version of the Genebank® data bank.

The sequences cloned and sequenced from these samples correspond, in particular, to two types of sequence: a first type of sequence, to be found in the majority of the clones (55% of the clones originating from the POL-2 isolates of the PLI-2 culture, and 67% of the clones originating from the MS7PG isolates of the LM7PC cultures), which corresponds to a family of "pol" sequences closely similar to, but different from, the endogenous human retrovirus designated ERV-9 or HSERV-9, and a second type of sequence which corresponds to sequences very strongly homologous to a sequence attributed to another infective and/or pathogenic agent designated MSRV-2.

The first type of sequence, representing the majority of the clones, consists of sequences whose variability enables four subfamilies of sequences to be defined. These subfamilies are sufficiently similar to one another for it to be possible to consider them to be quasi-species originating from the same retrovirus, as is well known for the HIV-1 retrovirus (14), or to be the outcome of interference with several endogenous proviruses coregulated in the producing cells. These more or less defective endogenous elements are sensitive to the same regulatory signals possibly generated by a replicative provirus, since they belong to the same family of endogenous retroviruses (15). This new family of endogenous retroviruses, or alternatively this new retroviral species from which the generation of quasi-species has been obtained in culture, and which contains a consensus of the sequences described below, is designated MSRV-1B.

Figure 1 presents the general consensus sequences of the sequences of the different MSRV-1B clones sequenced in this experiment, these sequences being identified, respectively, by SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5 and SEQ ID NO:6. These sequences display a homology with respect to nucleic acids ranging from 70% to 88% with the HSERV9 sequence referenced X57147 and M37638 in the Genebank® data base. Four "consensus" nucleic acid sequences representative of different quasi-species of a possibly exogenous retrovirus MSRV-1B, or of different subfamilies of an endogenous retrovirus MSRV-1B, have been defined. These representative consensus sequences are presented in Figure 2, with the translation into amino acids. A functional reading frame exists for each subfamily of these MSRV-1B sequences, and it can be seen that the functional open reading frame corresponds in each instance to the amino acid sequence appearing on the second line under the nucleic acid sequence. The general

consensus of the MSRV-1B sequence, identified by SEQ ID NO:7 and obtained by this PCR technique in the "pol" region, is presented in Figure 1.

The second type of sequence representing the majority of the clones sequenced is represented by the sequence MSRV-2B presented in Figure 3 and identified by SEQ ID NO:11. The differences observed in the sequences corresponding to the PCR primers are explained by the use of degenerate primers in mixture form used under different technical conditions.

The MSRV-2B sequence (SEQ ID NO:11) is sufficiently divergent from the retroviral sequences already described in the data banks for it to be suggested that the sequence region in question belongs to a new infective agent, designated MSRV-2. This infective agent would, in principle, on the basis of the analysis of the first sequences obtained, be related to a retrovirus but, in view of the technique used for obtaining this sequence, it could also be a DNA virus whose genome codes for an enzyme which incidentally possesses reverse transcriptase activity, as is the case, for example, with the hepatitis B virus, HBV (12). Furthermore, the random nature of the degenerate primers used for this PCR amplification technique may very well have permitted, as a result of unforeseen sequence homologies or of conserved sites in the gene for a related enzyme, the amplification of a nucleic acid originating from a prokaryotic or eukaryotic pathogenic and/or coinfective agent (protist).

EXAMPLE 2: OBTAINING CLONES DESIGNATED MSRV-1B AND MSRV-2B, DEFINING A FAMILY MSRV-1 and MSRV-2, BY "NESTED" PCR AMPLIFICATION OF THE CONSERVED POL REGIONS OF RETROVIRUSES ON PREPARATIONS OF B LYMPHOCYTES FROM A NEW CASE OF MS

The same PCR technique, modified according to the technique of Shih (12), was used to amplify and

sequence the RNA nucleic acid material present in a purified fraction of virions at the peak of "LM7-like" reverse transcriptase activity on a sucrose gradient according to the technique described by H. Perron (13), and according to the protocols mentioned in Example 1, from a spontaneous lymphoblastoid line obtained by self-immortalization in culture of B lymphocytes from an MS patient who was seropositive for the Epstein-Barr virus (EBV), after setting up the blood lymphoid cells in culture in a suitable culture medium containing a suitable concentration of cyclosporin A. A representation of the reverse transcriptase activity in the sucrose fractions taken from a purification gradient of the virions produced by this line is presented in Figure 4. Similarly, the culture supernatants of a B line obtained under the same conditions from a control free from MS were treated under the same conditions, and the assay of reverse transcriptase activity in the sucrose gradient fractions proved negative throughout (background), and is presented in Figure 5. Fraction 3 of the gradient corresponding to the MS B line and the same fraction without reverse transcriptase activity of the non-MS control gradient were analysed by the same RT-PCR technique as before, derived from Shih (12), followed by the same steps of cloning and sequencing as described in Example 1.

It is particularly noteworthy that the MSRV-1 and MSRV-2 type sequences are to be found only in the material associated with a peak of "LM7-like" reverse transcriptase activity originating from the MS B lymphoblastoid line. These sequences were not to be found with the material from the control (non-MS) B lymphoblastoid line in 26 recombinant clones taken at random. Only Mo-MuLV type contaminant sequences, originating from the commercial reverse transcriptase used for the cDNA synthesis step, and sequences without any particular retroviral analogy were to be found in this control, as a

result of the "consensus" amplification of homologous polymerase sequences which is produced by this PCR technique. Furthermore, the absence of a concentrated target which competes for the amplification reaction in the control sample permits the amplification of dilute contaminants. The difference in results is manifestly highly significant (chi-squared, p<0.001).

EXAMPLE 3: OBTAINING A CLONE PSJ17, DEFINING A RETROVIRUS MSRV-1, BY REACTION OF ENDOGENOUS REVERSE TRANSCRIPTASE WITH A VIRION PREPARATION ORIGINATING FROM THE PLI-2 LINE

This approach is directed towards obtaining reverse-transcribed DNA sequences from the supposedly retroviral RNA in the isolate using the reverse transcriptase activity present in this same isolate. This reverse transcriptase activity can theoretically function only in the presence of a retroviral RNA linked to a primer tRNA or hybridized with short strands of DNA already reverse-transcribed in the retroviral particles (16). Thus, the obtaining of specific retroviral sequences in a material contaminated with cellular nucleic acids was optimized according to these authors by means of the specific enzymatic amplification of the portions of viral RNAs with a viral reverse transcriptase activity. To this end, the authors determined the particular physicochemical conditions under which this enzymatic activity of reverse transcription on RNAs contained in virions could be effective in vitro. These conditions correspond to the technical description of the protocols presented below (endogenous RT reaction, purification, cloning and sequencing).

The molecular approach consisted in using a preparation of concentrated but unpurified virion obtained from the culture supernatants of the PLI-2 line, prepared according to the following method: the culture

supernatants are collected twice weekly, precentrifuged at 10,000 rpm for 30 minutes to remove cell debris and then frozen at -80°C or used as they are for the following steps. The fresh or thawed supernatants are centrifuged on a cushion of 30% glycerol-PBS at 100,000 g (or 30,000 rpm in a type 45 T LKB-HITACHI rotor) for 2 h at 4°C. After removal of the supernatant, the sedimented pellet is taken up in a small volume of PBS and constitutes the fraction of concentrated but unpurified virion. This concentrated but unpurified viral sample was used to perform a so-called endogenous reverse transcription reaction, as described below.

A volume of 200 ml of virion purified according to the protocol described above, and containing a reverse transcriptase activity of approximately 1-5 million dpm, is thawed at 37°C until a liquid phase appears, and then placed on ice. A 5-fold concentrated buffer was prepared with the following components: 500 mM Tris-HCl pH 8.2; 75 mM NaCl; 25 mM $MgCl_2$; 75 mM DTT and 0.10% NP 40; 100 ml of 5X buffer + 25 ml of a 100 mM solution of dATP + 25 ml of a 100 mM solution of dTTP + 25 ml of a 100 mM solution of dGTP + 25 ml of a 100 mM solution of dCTP + 100 ml of sterile distilled water + 200 ml of the virion suspension (RT activity of 5 million DPM) in PBS were mixed and incubated at 42°C for 3 hours. After this incubation, the reaction mixture is added directly to a buffered phenol/chloroform/isoamyl alcohol mixture (Sigma ref. P 3803); the aqueous phase is collected and one volume of sterile distilled water is added to the organic phase to re-extract the residual nucleic acid material. The collected aqueous phases are combined, and the nucleic acids contained are precipitated by adding 3M sodium acetate pH 5.2 to 1/10 volume + 2 volumes of ethanol + 1 ml of glycogen (Boehringer-Mannheim ref. 901 393) and placing the sample at -20°C for 4 h or overnight at +4°C. The precipitate obtained after centrifugation is then

washed with 70% ethanol and resuspended in 60 ml of distilled water. The products of this reaction were then purified, cloned and sequenced according to the protocol which will now be described: blunt-ended DNAs with unpaired adenines at the ends were generated: a "filling-in" reaction was first performed: 25 ml of the previously purified DNA solution were mixed with 2 ml of a 2.5 mM solution containing, in equimolar amounts, dATP + dGTP + dTTP + dCTP/1 ml of T4 DNA polymerase (Boehringer-Mannheim ref. 1004 786) / 5 ml of 10X "incubation buffer for restriction enzyme" (Boehringer-Mannheim ref. 1417 975) / 1 ml of a 1% bovine serum albumin solution / 16 ml of sterile distilled water. This mixture was incubated for 20 minutes at 11°C. 50 ml of TE buffer and 1 ml of glycogen (Boehringer-Mannheim ref. 901 393) were added thereto before extraction of the nucleic acids with phenol/chloroform/isoamyl alcohol (Sigma ref. P 3803) and precipitation with sodium acetate as described above. The DNA precipitated after centrifugation is resuspended in 10 ml of 10 mM Tris buffer pH 7.5. 5 ml of this suspension were then mixed with 20 ml of 5X Taq buffer, 20 ml of 5 mM dATP, 1 ml (5U) of Taq DNA polymerase (AmplitaqTM) and 54 ml of sterile distilled water. This mixture is incubated for 2 h at 75°C with a film of oil on the surface of the solution. The DNA suspended in the aqueous solution drawn off under the film of oil after incubation is precipitated as described above and resuspended in 2 ml of sterile distilled water. The DNA obtained was inserted into a plasmid using the TA CloningTM kit. The 2 ml of DNA solution were mixed with 5 ml of sterile distilled water, 1 ml of a 10-fold concentrated ligation buffer "10X LIGATION BUFFER", 2 ml of "pCR™ VECTOR" (25 ng/ml) and 1 ml of "TA DNA LIGASE". This mixture was incubated overnight at 12°C. The following steps were carried out according to the instructions of the TA Cloning™ kit (British Biotechnology). At the end of the procedure, the

white colonies of recombinant bacteria (white) were picked out in order to be cultured and to permit extraction of the plasmids incorporated according to the so-called "miniprep" procedure (17). The plasmid preparation from each recombinant colony was cut with a suitable restriction enzyme and analysed on agarose gel. Plasmids possessing an insert detected under UV light after staining the gel with ethidium bromide were selected for sequencing of the insert, after hybridization with a primer complementary to the Sp6 promoter present on the cloning plasmid of the TA cloning™ kit. The reaction prior to sequencing was then performed according to the method recommended for the use of the sequencing kit "Prism ready reaction kit dye deoxyterminator cycle sequencing kit" (Applied Biosystems, ref. 401384), and automatic sequencing was carried out with an Applied Biosystems "Automatic Sequencer, model 373 A" apparatus according to the manufacturer's instructions.

Discriminating analysis on the computerized data banks of the sequences cloned from the DNA fragments present in the reaction mixture enabled a retroviral type sequence to be revealed. The corresponding clone PSJ17 was completely sequenced, and the sequence obtained, presented in Figure 6 and identified by SEQ ID NO:9, was analysed using the "Geneworks®" software on the updated "Genebank™" data banks. An identical sequence already described could not be found by analysis of the data banks. Only a partial homology with some known retroviral elements was to be found. The most useful relative homology relates to an endogenous retrovirus designated ERV-9, or HSERV-9, according to the references (18).

EXAMPLE 4: PCR AMPLIFICATION OF THE NUCLEIC ACID SEQUENCE CONTAINED BETWEEN THE 5' REGION DEFINED BY THE CLONE "POL MSRV-1B" AND THE 3' REGION DEFINED BY THE CLONE PSJ17

Five oligonucleotides, M001, M002-A, M003-BCD, P004 and P005, were defined in order to amplify the RNA originating from purified POL-2 virions. Control reactions were performed so as to check for the presence of contaminants (reaction with water). The amplification consists of an RT-PCR step according to the protocol described in Example 2, followed by a "nested" PCR according to the PCR protocol described in the document EP-A-0,569,272. In the first RT-PCR cycle, the primers M001 and P004 or P005 are used. In the second PCR cycle, the primers M002-A or M003-BCD and the primer P004 are used. The primers are positioned as follows:

```
                 M002-A
                 M003-BCD
            M001 ____                    P004 P005
            ____ ____                    ____
________________________________________________ RNA
POL-2
<-------------->             <----------------------->
  pol MSRV-1B                           PSJ17
```

Their composition is:

primer M001: GGTCITICCICAIGG (SEQ ID NO:20)
primer M002-A: TTAGGGATAGCCCTCATCTCT (SEQ ID NO:21)
primer M003-BCD: TCAGGGATAGCCCCCATCTAT (SEQ ID NO:22)
primer P004: AACCCTTTGCCACTACATCAATTT (SEQ ID NO:23)
primer P005: GCGTAAGGACTCCTAGAGCTATT (SEQ ID NO:24)

The "nested" amplification product obtained, and designated M003-P004, is presented in Figure 7, and corresponds to the sequence SEQ ID NO:8.

EXAMPLE 5: AMPLIFICATION AND CLONING OF A PORTION OF THE MSRV-1 RETROVIRAL GENOME USING A SEQUENCE ALREADY IDENTIFIED, IN A SAMPLE OF VIRUS PURIFIED AT THE PEAK OF REVERSE TRANSCRIPTASE ACTIVITY

A PCR technique derived from the technique published by Frohman (19) was used. The technique derived makes it possible, using a specific primer at the 3' end of the genome to be amplified, to elongate the sequence towards the 5' region of the genome to be analysed. This technical variant is described in the documentation of the firm "Clontech Laboratories Inc.", (Palo-Alto California, USA) supplied with its product "5'-AmpliFINDERTM RACE Kit", which was used on a fraction of virion purified as described above.

The specific 3' primers used in the kit protocol for the synthesis of the cDNA and the PCR amplification are, respectively, complementary to the following MSRV-1 sequences:

cDNA:TCATCCATGTACCGAAGG (SEQ ID NO:25)
amplification :ATGGGGTTCCCAAGTTCCCT (SEQ ID NO:26)

The products originating from the PCR were obtained after purification on agarose gel according to conventional methods (17), and then resuspended in 10 ml of distilled water. Since one of the properties of Taq polymerase consists in adding an adenine at the 3' end of each of the two DNA strands, the DNA obtained was inserted directly into a plasmid using the TA CloningTM kit (British Biotechnology). The 2 ml of DNA solution were mixed with 5 ml of sterile distilled water, 1 ml of a 10-fold concentrated ligation buffer "10X LIGATION BUFFER", 2 ml of "pCR^{TM} VECTOR" (25 ng/ml) and 1 ml of "TA DNA LIGASE". This mixture was incubated overnight at 12°C. The following steps were carried out according to the instructions of the TA Cloning^{TM} kit (British Biotechnology). At the end of the procedure, the white

colonies of recombinant bacteria (white) were picked out in order to be cultured and to permit extraction of the plasmids incorporated according to the so-called "mini-prep" procedure (17). The plasmid preparation from each recombinant colony was cut with a suitable restriction enzyme and analysed on agarose gel. Plasmids possessing an insert detected under UV light after staining the gel with ethidium bromide were selected for sequencing of the insert, after hybridization with a primer complementary to the Sp6 promoter present on the cloning plasmid of the TA Cloning™ Kit. The reaction prior to sequencing was then performed according to the method recommended for the use of the sequencing kit "Prism ready reaction kit dye deoxyterminator cycle sequencing kit" (Applied Biosystems, ref. 401384), and automatic sequencing was carried out with an Applied Biosystems "Automatic Sequencer model 373 A" apparatus according to the manufacturer's instructions.

This technique was applied first to two fractions of virion purified as described below on sucrose from the "POL-2" isolate produced by the PLI-2 line on the one hand, and from the MS7PG isolate produced by the LM7PC line on the other hand. The culture supernatants are collected twice weekly, precentrifuged at 10,000 rpm for 30 minutes to remove cell debris and then frozen at -80°C or used as they are for the following steps. The fresh or thawed supernatants are centrifuged on a cushion of 30% glycerol-PBS at 100,000 g (or 30,000 rpm in a type 45 T LKB-HITACHI rotor) for 2 h at 4°C. After removal of the supernatant, the sedimented pellet is taken up in a small volume of PBS and constitutes the fraction of concentrated but unpurified virions. The concentrated virus is then applied to a sucrose gradient in sterile PBS buffer (15 to 50% weight/weight) and ultracentrifuged at 35,000 rpm (100,000 g) for 12 h at +4°C in a swing-out rotor. 10 fractions are collected, and 20 ml are withdrawn from

each fraction after homogenization to assay the reverse transcriptase activity therein according to the technique described by H. Perron (3). The fractions containing the peak of "LM7-like" RT activity are then diluted in sterile PBS buffer and ultracentrifuged for one hour at 35,000 rpm (100,000 g) to sediment the viral particles. The pellet of purified virion thereby obtained is then taken up in a small volume of a buffer which is appropriate for the extraction of RNA. The cDNA synthesis reaction mentioned above is carried out on this RNA extracted from purified extracellular virion. PCR amplification according to the technique mentioned above enabled the clone F1-11 to be obtained, whose sequence, identified by SEQ ID NO:2, is presented in Figure 8.

This clone makes it possible to define, with the different clones previously sequenced, a region of considerable length (1.2 kb) representative of the "pol" gene of the MSRV-1 retrovirus, as presented in Figure 9. This sequence, designated SEQ ID NO:1, is reconstituted from different clones overlapping one another at their ends, correcting the artefacts associated with the primers and with the amplification or cloning techniques which would artificially interrupt the reading frame of the whole. This sequence will be identified below under the designation "MSRV-1 pol* region". Its degree of homology with the HSERV-9 sequence is shown in Figure 12.

In Figure 9, the potential reading frame with its translation into amino acids is presented below the nucleic acid sequence.

EXAMPLE 6: DETECTION OF SPECIFIC MSRV-1 and MSRV-2 SEQUENCES IN DIFFERENT SAMPLES OF PLASMA ORIGINATING FROM PATIENTS SUFFERING FROM MS OR FROM CONTROLS

A PCR technique was used to detect the MSRV-1 and MSRV-2 genomes in plasmas obtained after taking blood

samples from patients suffering from MS and from non-MS controls onto EDTA.

Extraction of the RNAs from plasma was performed according to the technique described by P. Chomzynski (20), after adding one volume of buffer containing guanidinium thiocyanate to 1 ml of plasma stored frozen at -80°C after collection.

For MSRV-2, the PCR was performed under the same conditions and with the following primers:

- 5' primer, identified by SEQ ID NO:14
  5' GTAGTTCGATGTAGAAAGCG 3';
- 3' primer, identified by SEQ ID NO:15
  5' GCATCCGGCAACTGCACG 3'.

However, similar results were also obtained with the following PCR primers in two successive amplifications by "nested" PCR on samples of nucleic acids not treated with DNase.

The primers used for this first step of 40 cycles with a hybridization temperature of 48°C are the following:

- 5' primer, identified by SEQ ID NO:27
  5' GCCGATATCACCCGCCATGG 3', corresponding to a 5' MSRV-2 PCR primer, for a first PCR on samples from patients,
- 3' primer, identified by SEQ ID NO:28
  5' GCATCCGGCAACTGCACG 3', corresponding to a 3' MSRV-2 PCR primer, for a first PCR on samples from patients.

After this step, 10 ml of the amplification product are taken and used to carry out a second, so-called "nested" PCR amplification with primers located within the region already amplified. This second step takes place over 35 cycles, with a primer hybridization ("annealing") temperature of 50°C. The reaction volume is 100 ml.

The primers used for this second step are the following:

- 5' primer, identified by SEQ ID NO:29

5' CGCGATGCTGGTTGGAGAGC 3', corresponding to a 5' MSRV-2 PCR primer, for a nested PCR on samples from patients,

- 3' primer, identified by SEQ ID NO:30

5' TCTCCACTCCGAATATTCCG 3', corresponding to a 3' MSRV-2 PCR primer, for a nested PCR on samples from patients.

For MSRV-1, the amplification was performed in two steps. Furthermore, the nucleic acid sample is treated beforehand with DNase, and a control PCR without RT (AMV reverse transcriptase) is performed on the two amplification steps so as to verify that the RT-PCR amplification comes exclusively from the MSRV-1 RNA. In the event of a positive control without RT, the initial aliquot sample of RNA is again treated with DNase and amplified again.

The protocol for treatment with DNase lacking RNAse activity is as follows: the extracted RNA is aliquoted in the presence of "RNAse inhibitor" (Boehringer-Mannheim) in water treated with DEPC at a final concentration of 1 mg in 10 ml; to these 10 ml, 1 ml of "RNAse-free DNAse" (Boehringer-Mannheim) and 1.2 ml of pH 5 buffer containing 0.1 M/l sodium acetate and 5 mM/l $MgSO_4$ is added; the mixture is incubated for 15 min at 20°C and brought to 95°C for 1.5 min in a "thermocycler".

The first MSRV-1 RT-PCR step is performed according to a variant of the RNA amplification method as described in Patent Application No. EP-A-0,569,272. In particular, the cDNA synthesis step is performed at 42°C for one hour; the PCR amplification takes place over 40 cycles, with a primer hybridization ("annealing") temperature of 53°C. The reaction volume is 100 ml.

The primers used for this first step are the following:

- 5' primer, identified by SEQ ID NO:16
5' AGGAGTAAGGAAACCCAACGGAC 3';
- 3' primer, identified by SEQ ID NO:17
5' TAAGAGTTGCACAAGTGCG 3'.

After this step, 10 ml of the amplification product are taken and used to carry out a second, so-called "nested" PCR amplification with primers located within the region already amplified. This second step takes place over 35 cycles, with a primer hybridization ("annealing") temperature of 53°C. The reaction volume is 100 ml.

The primers used for this second step are the following:

- 5' primer, identified by SEQ ID NO:18
5' TCAGGGATAGCCCCCATCTAT 3';
- 3' primer, identified by SEQ ID NO:19
5' AACCCTTTGCCACTACATCAATTT 3'.

Figures 10 and 11 present the results of PCR in the form of photographs under ultraviolet light of ethidium bromide-impregnated agarose gels, in which an electrophoresis of the PCR amplification products applied separately to the different wells was performed.

The top photograph (Figure 10) shows the result of specific MSRV-2 amplification.

Well number 8 contains a mixture of DNA molecular weight markers, and wells 1 to 7 represent, in order, the products amplified from the total RNAs of plasmas originating from 4 healthy controls free from MS (wells 1 to 4) and from 3 patients suffering from MS at different stages of the disease (wells 5 to 7).

In this series, MSRV-2 nucleic acid material is detected in the plasma of one case of MS out of the 3 tested, and in none of the 4 control plasmas. Other

results obtained on more extensive series confirm these results.

The bottom photograph (Figure 11) shows the result of specific amplification by MSRV-1 "nested" RT-PCR:

well No. 1 contains the PCR product produced with water alone, without the addition of AMV reverse transcriptase; well No. 2 contains the PCR product produced with water alone, with the addition of AMV reverse transcriptase; well number 3 contains a mixture of DNA molecular weight markers; wells 4 to 13 contain, in order, the products amplified from the total RNAs extracted from sucrose gradient fractions (collected in a downward direction), on which gradient a pellet of virion originating from a supernatant of a culture infected with MSRV-1 and MSRV-2 was centrifuged to equilibrium according to the protocol described by H. Perron (13); to well 14 nothing was applied; to wells 15 to 17, the amplified products of RNA extracted from plasmas originating from 3 different patients suffering from MS at different stages of the disease were applied.

The MSRV-1 retroviral genome is indeed to be found in the sucrose gradient fraction containing the peak of reverse transcriptase activity measured according to the technique described by H. Perron (3), with a very strong intensity (fraction 5 of the gradient, placed in well No. 8). A slight amplification has taken place in the first fraction (well No. 4), probably corresponding to RNA released by lysed particles which floated at the surface of the gradient; similarly, aggregated debris has sedimented in the last fraction (tube bottom), carrying with it a few copies of the MSRV-1 genome which have given rise to an amplification of low intensity.

Of the 3 MS plasmas tested in this series, MSRV-1 RNA turned up in one case, producing a very intense amplification (well No. 17).

In this series, the MSRV-1 retroviral RNA genome, probably corresponding to particles of extracellular virus present in the plasma in extremely small numbers, was detected by "nested" RT-PCR in one case of MS out of the 3 tested. Other results obtained on more extensive series confirm these results.

Furthermore, the specificity of the sequences amplified by these PCR techniques may be verified and evaluated by the "ELOSA" technique as described by F. Mallet (21) and in the document FR-A-2,663,040.

For MSRV-1, the products of the nested PCR described above may be tested in two ELOSA systems enabling a consensus A and a consensus B+C+D of MSRV-1 to be detected separately, corresponding to the subfamilies described in Example 1 and Figures 1 and 2. In effect, the sequences closely resembling the consensus B+C+D are to be found essentially in the RNA samples originating from MSRV-1 virions purified from cultures or amplified in extracellular biological fluids of MS patients, whereas the sequences closely resembling the consensus A are essentially to be found in normal human cellular DNA.

The ELOSA/MSRV-1 system for the capture and specific hybridization of the PCR products of the subfamily A uses a capture oligonucleotide cpV1A with an amine bond at the 5' end and a biotinylated detection oligonucleotide dpV1A having as their sequence, respectively:

- cpV1A identified by SEQ ID NO:31

5' GATCTAGGCCACTTCTCAGGTCCAGS 3', corresponding to the ELOSA capture oligonucleotide for the products of MSRV-1 nested PCR performed with the primers identified by SEQ ID NO:16 and SEQ ID NO:17, optionally followed by amplification with the primers identified by SEQ ID NO:18 and SEQ ID NO:19 on samples from patients;

- dpV1A identified by SEQ ID NO:32;

5' CATCTITTTGGICAGGCAITAGC 3', corresponding to the ELOSA capture oligonucleotide for the subfamily A of the products of MSRV-1 "nested" PCR performed with the primers identified by SEQ ID NO:16 and SEQ ID NO:17, optionally followed by amplification with the primers identified by SEQ ID NO:18 and SEQ ID NO:19 on samples from patients.

The ELOSA/MSRV-1 system for the capture and specific hybridization of the PCR products of the subfamily B+C+D uses the same biotinylated detection oligonucleotide dpV1A and a capture oligonucleotide cpV1B with an amine bond at the 5' end having as its sequence:

- dpV1B identified by SEQ ID NO:33

5' CTTGAGCCAGTTCTCATACCTGGA 3', corresponding to the ELOSA capture oligonucleotide for the subfamily B + C + D of the products of MSRV-1 "nested" PCR performed with the primers identified by SEQ ID NO:16 and SEQ ID NO:17, optionally followed by amplification with the primers identified by SEQ ID NO:18 and SEQ ID NO:19 on samples from patients.

This ELOSA detection system enabled it to be verified that none of the PCR products thus amplified from DNase-treated plasmas of MS patients contained a sequence of the subfamily A, and that all were positive with the consensus of the subfamilies B, C and D.

For MSRV-2, a similar ELOSA technique was evaluated on isolates originating from infected cell cultures, using the following PCR amplification primers,

- 5' primer, identified by SEQ ID NO:34

5' AGTGYTRCCMCARGGCGCTGAA 3', corresponding to a 5' MSRV-2 PCR primer, for PCR on samples from cultures,

- 3' primer, identified by SEQ ID NO:35

5' GMGGCCAGCAGSAKGTCATCCA 3', corresponding to a 3' MSRV-2 PCR primer, for PCR on samples from cultures,

and the capture oligonucleotides with an amine bond at the 5' end cpV2 and the biotinylated detection oligonucleotide dpV2 having as their respective sequences:

- cpV2 identified by SEQ ID NO:36

5 GGATGCCGCCTATAGCCTCTAC 3', corresponding to an ELOSA capture oligonucleotide for the products of MSRV-2 PCR performed with the primers SEQ ID NO:34 and SEQ ID NO:35, or optionally with the degenerate primers defined by Shih (12).

- dpV2 identified by SEQ ID NO:37

5' AAGCCTATCGCGTGCAGTTGCC 3', corresponding to an ELOSA detection oligonucleotide for the products of MSRV-2 PCR performed with the primers SEQ ID NO:34 and SEQ ID NO:35, or optionally with the degenerate primers defined by Shih (12)

This PCR amplification system with a pair of primers different from those which were described previously for amplification on the samples from patients made it possible to confirm the infection with MSRV-2 of in vitro cultures and of samples of nucleic acids used for the molecular biology studies.

All things considered, the first results of PCR detection of the genome of pathogenic and/or infective agents show that it is possible that free "virus" may circulate in the blood stream of patients in an acute, virulent phase, outside the nervous system. This is compatible with the almost invariable presence of "gaps" in the blood-brain barrier of patients in an active phase of MS.

EXAMPLE 7: OBTAINING SEQUENCES OF THE "env" GENE OF THE MSRV-1 RETROVIRAL GENOME

As has already been described in Example 5, a PCR technique derived from the technique published by Frohman (19) was used. The technique derived makes it possible, using a specific primer at the 3' end of the

genome to be amplified, to elongate the sequence towards the 5' region of the genome to be analysed. This technical variant is described in the documentation of "Clontech Laboratories Inc., (Palo-Alto California, USA) supplied with its product "5'-AmpliFINDER^{TM} RACE Kit", which was used on a fraction of virion purified as described above.

In order to carry out an amplification of the 3' region of the MSRV-1 retroviral genome encompassing the region of the "env" gene, a study was carried out to determine a consensus sequence in the LTR regions of the same type as those of the defective endogenous retrovirus HSERV-9 (18, 24), with which the MSRV-1 retrovirus displays partial homologies.

The same specific 3' primer was used in the kit protocol for the synthesis of the cDNA and the PCR amplification; its sequence is as follows:

GTGCTGATTGGTGTATTTACAATCC (SEQ ID NO 45)

Synthesis of the complementary DNA (cDNA) and unidirectional PCR amplification with the above primer were carried out in one step according to the method described in Patent EP-A-0,569,272.

The products originating from the PCR were extracted after purification of agarose gel according to conventional methods (17), and then resuspended in 10 ml of distilled water. Since one of the properties of Taq polymerase consists in adding an adenine at the 3' end of each of the two DNA strands, the DNA obtained was inserted directly into a plasmid using the TA Cloning^{TM} kit (British Biotechnology). The 2 ml of DNA solution were mixed with 5 ml of sterile distilled water, 1 ml of a 10-fold concentrated ligation buffer "10X LIGATION BUFFER", 2 ml of "pCR^{TM} VECTOR" (25 ng/ml) and 1 ml of "TA DNA LIGASE". This mixture was incubated overnight at 12°C. The following steps were carried out according to the instructions of the TA Cloning® kit (British Biotechnology). At the end of the procedure, the white colonies of

recombinant bacteria (white) were picked out in order to be cultured and to permit extraction of the plasmids incorporated according to the so-called "miniprep" procedure (17). The plasmid preparation from each recombinant colony was cut with a suitable restriction enzyme and analysed on agarose gel. Plasmids possessing an insert detected under UV light after staining the gel with ethidium bromide were selected for sequencing of the insert, after hybridization with a primer complementary to the Sp6 promoter present on the cloning plasmid of the TA Cloning™ Kit. The reaction prior to sequencing was then performed according to the method recommended for the use of the sequencing kit "Prism ready reaction kit dye deoxyterminator cycle sequencing kit" (Applied Biosystems, ref. 401384), and automatic sequencing was carried out with an Applied Biosystems "automatic sequencer, model 373 A" apparatus according to the manufacturer's instructions.

This technical approach was applied to a sample of virion concentrated as described below from a mixture of culture supernatants produced by B lymphoblastoid lines such as are described in Example 2, established from lymphocytes of patients suffering from MS and possessing reverse transcriptase activity which is detectable according to the technique described by Perron et al. (3): the culture supernatants are collected twice weekly, precentrifuged at 10,000 rpm for 30 minutes to remove cell debris and then frozen at -80°C or used as they are for the following steps. The fresh or thawed supernatants are centrifuged on a cushion of 30% glycerol-PBS at 100,000 g for 2 h at 4°C. After removal of the supernatant, the sedimented pellet constitutes the sample of concentrated but unpurified virions. The pellet thereby obtained is then taken up in a small volume of an appropriate buffer for the extraction of RNA. The cDNA synthesis reaction

mentioned above is carried out on this RNA extracted from concentrated extracellular virion.

RT-PCR amplification according to the technique mentioned above enabled the clone FBd3 to be obtained, whose sequence, identified by SEQ ID NO:46, is presented in Figure 13.

In Figure 14, the sequence homology between the clone FBd3 and the HSERV-9 retrovirus is shown on the matrix chart by a continuous line for any partial homology greater than or equal to 65%. It can be seen that there are homologies in the flanking regions of the clone (with the pol gene at the 5' end and with the env gene and then the LTR at the 3' end), but that the internal region is totally divergent and does not display any homology, even weak, with the "env" gene of HSERV9. Furthermore, it is apparent that the clone FBd3 contains a longer "env" region than the one which is described for the defective endogenous HSERV-9; it may thus be seen that the internal divergent region constitutes an "insert" between the regions of partial homology with the HSERV-9 defective genes.

EXAMPLE 8: AMPLIFICATION, CLONING AND SEQUENCING OF THE REGION OF THE MSRV-1 RETROVIRAL GENOME LOCATED BETWEEN THE CLONES PSJ17 AND FBd3

Four oligonucleotides, F1, B4, F6 and B1, were defined for amplifying RNA originating from concentrated virions of the strains POL2 and MS7PG. Control reactions were performed so as to check for the presence of contaminants (reaction with water). The amplification consists of a first step of RT-PCR according to the protocol described in Patent Application EP-A-0,569,272, followed by a second step of PCR performed on 10 ml of product of the first step with primers internal to the amplified first region ("nested" PCR). In the first RT-PCR cycle, the primers F1 and B4 are used. In the second PCR

cycle, the primers F6 and the primer B1 are used. The primers are positioned as follows:

```
         F1   F6                    B1    B4

         ___  ___                   ___   ___
_____________________________________________________RNA
MSRV-1

PSJ17                         FBd3
---------->          <------------------/---
5'pol MSRV-1         3' pol MSRV-1      /
5'env
```

Their composition is:

primer F1: TGATGTGAACGGCATACTCACTG (SEQ ID NO:47)
primer B4: CCCAGAGGTTAGGAACTCCCTTTC (SEQ ID NO 48)
primer F6: GCTAAAGGAGACTTGTGGTTGTCAG (SEQ ID NO 49)
primer B1: CAACATGGGCATTTCGGATTAG (SEQ ID NO 50)

The product of "nested" amplification obtained and designated "t pol" is presented in Figure 15, and corresponds to the sequence SEQ ID NO:51.

EXAMPLE 9: OBTAINING NEW SEQUENCES, EXPRESSED AS RNA IN CELLS IN CULTURE PRODUCING MSRV-1, AND COMPRISING AN "env" REGION OF THE MSRV-1 RETROVIRAL GENOME

A library of cDNA was produced according to the procedure described by the manufacturer of the "cDNA synthesis module, cDNA rapid adaptator ligation module, cDNA rapid cloning module and lambda gt10 in vitro packaging module" kits (Amersham, ref RPN1256Y/Z, RPN1712, RPN1713, RPN1717, N334Z), from the messenger RNA extracted from cells of a B lymphoblastoid line such as is described in Example 2, established from the lymphocytes of a patient suffering from MS and possessing reverse transcriptase activity which is detectable according to the technique described by Perron et al. (3).

Oligonucleotides were defined for amplifying the cDNA cloned into the nucleic acid library between the 3' region of the clone PSJ17 (pol) and the 5'(LTR) region of the clone FBd3. Control reactions were performed so as to check for the presence of contaminants (reaction with water). PCR reactions performed on the nucleic acids cloned into the library with different pairs of primers enabled a series of clones linking pol sequences to the MSRV-1 type env or LTR sequences to be amplified.

Two clones are representative of the sequences obtained in the cellular cDNA library:

- the clone JLBc1, whose sequence SEQ ID NO:52 is presented in Figure 16;
- the clone JLBc2, whose sequence SEQ ID NO:53 is presented in Figure 17.

The sequences of the clones JLBc1 and JLBc2 are homologous to that of the clone FBd3, as is apparent in Figures 18 and 19. The homology between the clone JLBc1 and the clone JLBc2 is shown in Figure 20.

The homologies between the clones JLBc1 and JLBc2 on the one hand and the HSERV9 sequence on the other hand are presented, respectively, in Figures 21 and 22.

It will be noted that the region of homology between JLB1, JLB2 and FBd3 comprises, with a few sequence and size variations of the "insert", the additional sequence absent ("inserted") in the HSERV-9 env sequence, as described in Example 8.

It will also be noted that the cloned "pol" region is very homologous to HSERV-9, does not possess a reading frame (bearing in mind the sequence errors induced by the techniques used, including even the automatic sequencer) and diverges from the MSRV-1 sequences obtained from virions. In view of the fact that these sequences were cloned from the RNA of cells expressing MSRV-1 particles, it is probable that they originate from endogenous retroviral elements related to the ERV9 family;

this is all the more likely for the fact that the pol and env genes are present on the same RNA which is clearly not the MSRV-1 genomic RNA. Some of these ERV9 elements possess functional LTRs which can be activated by replicative viruses coding for homologous or heterologous transactivators. Under these conditions, the relationship between MSRV-1 and HSERV-9 makes probable the transactivation of the defective (or otherwise) endogenous ERV9 elements by homologous, or even identical, MSRV-1 transactivating proteins.

Such a phenomenon may induce a viral interference between the expression of MSRV-1 and the related endogenous elements. Such an interference generally leads to a so-called "defective-interfering" expression, some features of which were to be found in the MSRV-1-infected cultures studied. Furthermore, such a phenomenon does not lack generation of the expression of polypeptides, or even of endogenous retroviral proteins which are not necessarily tolerated by the immune system. Such a scheme of aberrant expression of endogenous elements related to MSRV-1 and induced by the latter is liable to multiply the aberrant antigens, and hence to contribute to the induction of autoimmune processes such as are observed in MS.

It is, however, essential to note that the clones JLBc1 and JLBc2 differ from the ERV9 or HSERV9 sequence already described, in that they possess a longer env region comprising an additional region totally divergent from ERV9. Their kinship with the endogenous ERV9 family may hence be defined, but they clearly constitute novel elements never hitherto described. In effect, interrogation of the data banks of nucleic acid sequences available in version No. 15 (1995) of the "Entrez" software (NCBI, NIH, Bethesda, USA) did not enable a known homologous sequence in the env region of these clones to be identified.

EXAMPLE 10: OBTAINING SEQUENCES LOCATED IN THE 5' pol AND 3' gag REGION OF THE MSRV-1 RETROVIRAL GENOME

As has already been described in Example 5, a PCR technique derived from the technique published by Frohman (19) was used. The technique derived makes it possible, using a specific primer at the 3' end of the genome to be amplified, to elongate the sequence towards the 5' region of the genome to be analysed. This technical variant is described in the documentation of the firm Clontech Laboratories Inc., (Palo-Alto California, USA) supplied with its product "5'-AmpliFINDER™ RACE Kit", which was used on a fraction of virion purified as described above.

In order to carry out an amplification of the 5' region of the MSRV-1 retroviral genome starting from the pol sequence already sequenced (clone F11-1) and extending towards the gag gene, MSRV-1 specific primers were defined.

The specific 3' primers used in the kit protocol for the synthesis of the cDNA and the PCR amplification are, respectively, complementary to the following MSRV-1 sequences:

cDNA: (SEQ ID NO:54)
CCTGAGTTCTTGCACTAACCC
amplification: (SEQ ID NO:55)
GTCCGTTGGGTTTCCTTACTCCT

The products originating from the PCR were extracted after purification on agarose gel according to conventional methods (17), and then resuspended in 10 ml of distilled water. Since one of the properties of Taq polymerase consists in adding an adenine at the 3' end of each of the two DNA strands, the DNA obtained was inserted directly into a plasmid using the TA Cloning™ kit (British Biotechnology). The 2 ml of DNA solution were mixed with 5 ml of sterile distilled water, 1 ml of a 10-fold

concentrated ligation buffer "10X LIGATION BUFFER", 2 ml of "pCR™ VECTOR" (25 ng/ml) and 1 ml of "TA DNA LIGASE". This mixture was incubated overnight at 12°C. The following steps were carried out according to the instructions of the TA Cloning® kit (British Biotechnology). At the end of the procedure, the white colonies of recombinant bacteria (white) were picked out in order to be cultured and to permit extraction of the plasmids incorporated according to the so-called "miniprep" procedure (17). The plasmid preparation from each recombinant colony was cut with a suitable restriction enzyme and analysed on agarose gel. Plasmids possessing an insert detected under UV light after staining the gel with ethidium bromide were selected for sequencing of the insert, after hybridization with a primer complementary to the Sp6 promoter present on the cloning plasmid of the TA Cloning™ Kit. The reaction prior to sequencing was then performed according to the method recommended for the use of the sequencing kit "Prism ready reaction kit dye deoxyterminator cycle sequencing kit" (Applied Biosystems, ref. 401384), and automatic sequencing was carried out with an Applied Biosystems "automatic sequencer model 373 A" apparatus according to the manufacturer's instructions.

This technical approach was applied to a sample of virion concentrated as described below from a mixture of culture supernatants produced by B lymphoblastoid lines such as are described in Example 2, established from lymphocytes of patients suffering from MS and possessing reverse transcriptase activity which is detectable according to the technique described by Perron et al. (3): the culture supernatants are collected twice weekly, precentrifuged at 10,000 rpm for 30 minutes to remove cell debris and then frozen at -80°C or used as they are for the following steps. The fresh or thawed supernatants are centrifuged on a cushion of 30% glycerol-PBS at 100,000 g

for 2 h at 4°C. After removal of the supernatant, the sedimented pellet constitutes the sample of concentrated but unpurified virions. The pellet thereby obtained is then taken up in a small volume of an appropriate buffer for the extraction of RNA. The cDNA synthesis reaction mentioned above is carried out on this RNA extracted from concentrated extracellular virion.

RT-PCR amplification according to the technique mentioned above enabled the clone GM3 to be obtained, whose sequence, identified by SEQ ID NO 56, is presented in Figure 23.

In Figure 24, the sequence homology between the clone GMP3 and the HSERV-9 retrovirus is shown on the matrix chart by a continuous line, for any partial homology greater than or equal to 65%.

In summary, Figure 25 shows the localization of the different clones studied above, relative to the known ERV9 genome. In Figure 25, since the MSRV-1 env region is longer than the reference ERV9 env gene, the additional region is shown above the point of insertion according to a "V", on the understanding that the inserted material displays a sequence and size vari-ability between the clones shown (JLBc1, JLBc2, FBd3). And Figure 26 shows the position of different clones studied in the MSRV-1 pol* region.

By means of the clone GM3 described above, a possible reading frame could be defined, covering the whole of the pol gene, referenced according to SEQ ID NO:57, shown in the successive Figures 27a to 27c.

EXAMPLE 11: DETECTION OF ANTI-MSRV-1 SPECIFIC ANTIBODIES IN HUMAN SERUM

Identification of the sequence of the pol gene of the MSRV-1 retrovirus and of an open reading frame of this gene enabled the amino acid sequence SEQ ID NO:39 of

a region of the said gene, referenced SEQ ID NO:40, to be determined (see Figure 28).

Different synthetic peptides corresponding to fragments of the protein sequence of MSRV-1 reverse transcriptase encoded by the pol gene were tested for their antigenic specificity with respect to sera of patients suffering from MS and of healthy controls.

The peptides were synthesized chemically by solid-phase synthesis according to the Merrifield technique (Barany G, and Merrifielsd R.B, 1980, In the Peptides, 2, 1-284, Gross E and Meienhofer J, Eds., Academic Press, New York). The practical details are those described below.

a) Peptide synthesis:

The peptides were synthesized on a phenylacetamidomethyl (PAM)/polystyrene/divinylbenzene resin (Applied Biosystems, Inc. Foster City, CA), using an "Applied Biosystems 430A" automatic synthesizer. The amino acids are coupled in the form of hydroxybenzotriazole (HOBT) esters. The amino acids used are obtained from Novabiochem (Läuflerlfingen, Switzerland) or Bachem (Bubendorf, Switzerland).

The chemical synthesis was performed using a double coupling protocol with N-methylpyrrolidone (NMP) as solvent. The peptides were cut from the resin, as well as the side-chain protective groups, simultaneously, using hydrofluoric acid (HF) in a suitable apparatus (type I cleavage apparatus, Peptide Institute, Osaka, Japan).

For 1 g of peptidyl resin, 10 ml of HF, 1 ml of anisole and 1 ml of dimethyl sulphide 5DMS are used. The mixture is stirred for 45 minutes at -2°C. The HF is then evaporated off under vacuum. After intensive washes with ether, the peptide is eluted from the resin with 10% acetic acid and then lyophilized.

The peptides are purified by preparative high performance liquid chromatography on a VYDAC C18 type

column (250 x 21 mm) (The Separation Group, Hesperia, CA, USA). Elution is carried out with an acetonitrile gradient at a flow rate of 22 ml/min. The fractions collected are monitored by an elution under isocratic conditions on a VYDAC® C18 analytical column (250 x 4.6 mm) at a flow rate of 1 ml/min. Fractions having the same retention time are pooled and lyophilized. The preponderant fraction is then analysed by analytical high performance liquid chromatography with the system described above. The peptide which is considered to be of acceptable purity manifests itself in a single peak representing not less than 95% of the chromatogram.

The purified peptides are then analysed with the object of monitoring their amino acid composition, using an Applied Biosystems 420H automatic amino acid analyser. Measurement of the (average) chemical molecular mass of the peptides is obtained using LSIMS mass spectrometry in the positive ion mode on a VG. ZAB.ZSEQ double focusing instrument connected to a DEC-VAX 2000 acquisition system (VG analytical Ltd, Manchester, England).

The reactivity of the different peptides was tested against sera of patients suffering from MS and against sera of healthy controls. This enabled a peptide designated POL2B to be selected, whose sequence is shown in Figure 28 in the identifier SEQ ID NO:39, below, encoded by the pol gene of MSRV-1 (nucleotides 181 to 330).

b) Antigenic properties:

The antigenic properties of the POL2B peptide were demonstrated according to the ELISA protocol described below.

The lyophilized POL2B peptide was dissolved in sterile distilled water at a concentration of 1 mg/ml. This stock solution was aliquoted and kept at +4°C for use over a fortnight, or frozen at -20°C for use within 2 months. An aliquot is diluted in PBS (phosphate buffered

saline) solution so as to obtain a final peptide concentration of 1 microgram/ml. 100 microlitres of this dilution are placed in each well of microtitration plates ("high-binding" plastic, COSTAR ref: 3590). The plates are covered with a "plate-sealer" type adhesive and kept overnight at +4°C for the phase of adsorption of the peptide to the plastic. The adhesive is removed and the plates are washed three times with a volume of 300 microlitres of a solution A (1X PBS, 0.05% Tween 20®), then inverted over an absorbent tissue. The plates thus drained are filled with 200 microlitres per well of a solution B (solution A + 10% of goat serum), then covered with an adhesive and incubated for 45 minutes to 1 hour at 37°C. The plates are then washed three times with the solution A as described above.

The test serum samples are diluted beforehand to 1/50 in the solution B, and 100 microlitres of each dilute test serum are placed in the wells of each microtitration plate. A negative control is placed in one well of each plate, in the form of 100 microlitres of buffer B. The plates covered with an adhesive are then incubated for 1 to 3 hours at 37°C. The plates are then washed three times with the solution A as described above. In parallel, a peroxidase-labelled goat antibody directed against human IgG (Sigma Immunochemicals ref. A6029) or IgM (Cappel ref. 55228) is diluted in the solution B (dilution 1/5000 for the anti-IgG and 1/1000 for the anti-IgM). 100 microlitres of the appropriate dilution of the labelled antibody are then placed in each well of the microtitration plates, and the plates covered with an adhesive are incubated for 1 to 2 hours at 37°C. A further washing of the plates is then performed as described above. In parallel, the peroxidase substrate is prepared according to the directions of the "Sigma fast OPD kit" (Sigma Immunochemicals, ref. P9187). 100 microlitres of substrate solution are placed in each

well, and the plates are placed protected from light for 20 to 30 minutes at room temperature.

When the colour reaction has stabilized, the plates are placed immediately in an ELISA plate spectrophotometric reader, and the optical density (OD) of each well is read at a wavelength of 492 nm. Alternatively, 30 microlitres of 1N HCl are placed in each well to stop the reaction, and the plates are read in the spectrophotometer within 24 hours.

The serological samples are introduced in duplicate or in triplicate, and the optical density (OD) corresponding to the serum tested is calculated by taking the mean of the OD values obtained for the same sample at the same dilution.

The net OD of each serum corresponds to the mean OD of the serum minus the mean OD of the negative control (solution B: PBS, 0.05% Tween 20®, 10% goat serum).

c) Detection of anti-MSRV-1 IgG antibodies by ELISA:

The technique described above was used with the POLB2 peptide to test for the presence of anti-MSRV-1 specific IgG antibodies in the serum of 29 patients for whom a definite or probable diagnosis of MS was established according to the criteria of Poser (23), and of 32 healthy controls (blood donors).

Figure 29 shows the results for each serum tested with an anti-IgG antibody. Each vertical bar represents the net optical density (OD at 492 nm) of a serum tested. The ordinate axis gives the net OD at the top of the vertical bars. The first 29 vertical bars lying to the left of the vertical broken line represent the sera of 29 cases of MS tested, and the 32 vertical bars lying to the right of the vertical broken line represent the sera of 32 healthy controls (blood donors).

The mean of the net OD values for the MS sera tested is 0.62. The diagram enables 5 controls to be

revealed whose net OD rises above the grouped values of the control population. These values may represent the presence of specific IgGs in symptomless seropositive patients. Two methods were hence evaluated in order to determine the statistical threshold of positivity of the test.

The mean of the net OD values for the controls, including the controls with high net OD values, is 0.36. Without the 5 controls whose net OD values are greater than or equal to 0.5, the mean of the "negative" controls is 0.33. The standard deviation of the negative controls is 0.10. A theoretical threshold of positivity may be calculated according to the formula:
threshold value (mean of the net OD values of the seronegative controls) + (2 or 3 x standard deviation of the net OD values of the seronegative controls).

In the first case, there are considered to be symptomless seropositives, and the threshold value is equal to 0.33 + (2 x 0.10) = 0.53. The negative results represent a non-specific "background" of the presence of antibodies directed specifically against an epitope of the peptide.

In the second case, if the set of controls consisting of blood donors in apparent good health is taken as a reference basis, without excluding the sera which are, on the face of it, seropositive, the standard deviation of the "non-MS controls" is 0.116. The threshold value then becomes 0.36 + (2 x 0.116) = 0.59.

According to this analysis, the test is specific for MS. In this respect, it is seen that the test is specific for MS, since, as shown in Table 1, no control has a net OD above this threshold. In fact, this result reflects the fact that the antibody titres in patients suffering from MS are, for the most part, higher than in healthy controls who have been in contact with MSRV-1.

TABLE No. 1

	MS	CONTROLS
	0.681	0.3515
	1.0425	0.56
	0.5675	0.3565
	0.63	0.449
	0.588	0.2825
	0.645	0.55
	0.6635	0.52
	0.576	0.2535
	0.7765	0.55
	0.5745	0.51
	0.513	0.426
	0.4325	0.451
	0.7255	0.227
	0.859	0.3905
	0.6435	0.265
	0.5795	0.4295
	0.8655	0.291
	0.671	0.347
	0.596	0.4495
	0.662	0.3725
	0.602	0.181
	0.525	0.2725
	0.53	0.426
	0.565	0.1915
	0.517	0.222
	0.607	0.395
	0.3705	0.34
	0.397	0.307
	0.4395	0.219
		0.491
		0.2265
		0.2605
MEAN	0.62	0.33
STD DEV	0.14	0.10
THRESHOLD VALUE		0.53

In accordance with the first method of calculation, and as shown in Figure 29 and in the corresponding Table 1, 26 of the 29 MS sera give a positive result (net OD greater than or equal to 0.50), indicating the presence of IgGs specifically directed against the POL2B peptide, hence against a portion of the reverse transcriptase enzyme of the MSRV-1 retrovirus encoded by its pol gene, and consequently against the MSRV-1 retrovirus. Thus, approximately 90% of the MS patients tested have reacted against an epitope carried by the POL2B peptide and possess circulating IgGs directed against the latter.

Five out of 32 blood donors in apparent good health show a positive result. Thus, it is apparent that approximately 15% of the symptomless population may have been in contact with an epitope carried by the POL2B peptide under conditions which have led to an active immunization which manifests itself in the persistence of specific serum IgGs. These conditions are compatible with an immunization against the MSRV-1 retrovirus reverse transcriptase during an infection with (and/or reactivation of) the MSRV-1 retrovirus. The absence of apparent neurological pathology recalling MS in these seropositive controls may indicate that they are healthy carriers and have eliminated an infectious virus after immunizing themselves, or that they constitute an at-risk population of chronic carriers. In effect, epidemiological data showing that a pathogenic agent present in the environment of regions of high prevalence of MS may be the cause of this disease imply that a fraction of the population free from MS has necessarily been in contact with such a pathogenic agent. It has been shown that the MSRV-1 retrovirus constitutes all or part of this "pathogenic agent" at the source of MS, and it is hence normal for controls taken from a healthy population to possess IgG type antibodies against components of the MSRV-1 retrovirus. Thus, the difference in seroprevalence between

the MS and control populations is extremely significant: "chi-squared" test, $p < 0.001$. These results hence point to an aetiopathogenic role of MSRV-1 in MS.

d) Detection of anti-MSRV-1 IgM antibodies by ELISA:

The ELISA technique with the POL2B peptide was used to test for the presence of anti-MSRV-1 IgM specific antibodies in the serum of 36 patients for whom a definite or probable diagnosis of MS was established according to the criteria of Poser (23), and of 42 healthy controls (blood donors).

Figure 30 shows the results for each serum tested with an anti-IgM antibody. Each vertical bar represents the net optical density (OD at 492 nm) of a serum tested. The ordinate axis gives the net OD at the top of the vertical bars. The first 36 vertical bars lying to the left of the vertical line cutting the abscissa axis represent the sera of 36 cases of MS tested, and the vertical bars lying to the right of the vertical broken line represent the sera of 42 healthy controls (blood donors). The horizontal line drawn in the middle of the diagram represents a theoretical threshold defining the boundary of the positive results (in which the top of the bar lies above) and the negative results (in which the top of the bar lies below).

The mean of the net OD values for the MS cases tested is 0.19.

The mean of the net OD values for the controls is 0.09.

The standard deviation of the negative controls is 0.05.

In view of the small difference between the mean and the standard deviation of the controls, the threshold of theoretical positivity may be calculated according to the formula:

threshold value = (mean of the net OD values of the seronegative controls) + (3 x standard deviation of the net OD values of the seronegative controls).

The threshold value is hence equal to 0.09 + (3 x 0.05) = 0.26; or, in practice, 0.25.

The negative results represent a non-specific "background" of the presence of antibodies directed specifically against an epitope of the peptide.

According to this analysis, and as shown in Figure 30 and in the corresponding Table 2, the IgM test is specific for MS, since no control has a net OD above the threshold. 7 of the 36 MS sera produce a positive IgM result; now, a study of the clinical data reveals that these positive sera were taken during a first attack of MS or an acute attack in untreated patients. It is known that IgMs directed against pathogenic agents are produced during primary infections or during reactivations following a latency phase of the said pathogenic agent.

The difference in seroprevalence between the MS and control populations is extremely significant: "chi-squared" test, $p < 0.001$.

These results point to an aetiopathogenic role of MSRV-1 in MS.

The detection of IgM and IgG antibodies against the POL2B peptide enables the course of an MSRV-1 infection and/or of the viral reactivation of MSRV-1 to be evaluated.

TABLE No. 2

	MS	CONTROLS
	0.064	0.243
	0.087	0.11
	0.044	0.098
	0.115	0.028
	0.089	0.094
	0.025	0.038
	0.097	0.176
	0.108	0.146
	0.018	0.049
	0.234	0.161
	0.274	0.113
	0.225	0.079
	0.314	0.093
	0.522	0.127
	0.306	0.02
	0.143	0.052
	0.375	0.062
	0.142	0.074
	0.157	0.043
	0.168	0.046
	1.051	0.041
	0.104	0.13
	0.187	0.153
	0.044	0.107
	0.053	0.178
	0.153	0.114
	0.07	0.078
	0.033	0.118
	0.104	0.177
	0.187	0.026
	0.044	0.024
	0.053	0.046
	0.153	0.116
	0.07	0.04
	0.033	0.028
	0.973	0.073
		0.008
		0.074
		0.141
		0.219
		0.047
		0.017
MEAN	0.19	0.09
STD. DEV.	0.23	0.05
THRESHOLD VALUE		0.26

e) Search for immunodominant epitopes in the POL2B peptide:

In order to reduce the non-specific background and to optimize the detection of the responses of the anti-MSRV-1 antibodies, the synthesis of octapeptides, advancing in successive one amino acid steps, covering the whole of the sequence determined by POL2B, was carried out according to the protocol described below.

The chemical synthesis of overlapping octapeptides covering the amino acid sequence 61-110 shown in the identifier SEQ ID NO:39 was carried out on an activated cellulose membrane according to the technique of BERG et al. (1989. J. Ann. Chem. Soc., 111, 8024-8026) marketed by Cambridge Research Biochemicals under the trade name Spotscan. This technique permits the simultaneous synthesis of a large number of peptides and their analysis.

The synthesis is carried out with esterified amino acids in which the a-amino group is protected with an FMOC group (Nova Biochem) and the side-chain groups with protective groups such as trityl, t-butyl ester or t-butyl ether. The esterified amino acids are solubilized in N-methylpyrrolidone (NMP) at a concentration of 300 nM, and 0.9 ml are applied to spots of deposit of bromophenol blue. After incubation for 15 minutes, a further application of amino acids is carried out according to another 15-minute incubation. If the coupling between two amino acids has taken place correctly, a coloration modification (change from blue to yellow-green) is observed. After three washes in DMF, an acetylation step is performed with acetic anhydride. Next, the terminal amino groups of the peptides in the process of synthesis are deprotected with 20% pyridine in DMF. The spots of deposit are restained with a 1% solution of bromophenol blue in DMF, washed three times with methanol and dried. This set of operations constitutes one cycle of addition

of an amino acid, and this cycle is repeated until the synthesis is complete. When all the amino acids have been added, the NH2-terminal group of the last amino acid is deprotected with 20% piperidine in DMF and acetylated with acetic anhydride. The groups protecting the side chain are removed with a dichloromethane/trifluoroacetic acid/triisobutylsilane (5 ml/5 ml/250 ml) mixture. The immunoreactivity of the peptides is then tested by ELISA.

After synthesis of the different octapeptides in duplicate on two different membranes, the latter are rinsed with methanol and washed in TBS (0.1M Tris pH 7.2), then incubated overnight at room temperature in a saturation buffer. After several washes in TBS-T (0.1M Tris pH 7.2 - 0.05% Tween 20), one membrane is incubated with a 1/50 dilution of a reference serum originating from a patient suffering from MS, and the other membrane with a 1/50 dilution of a pool of sera of healthy controls. The membranes are incubated for 4 hours at room temperature. After washes with TBS-T, a β-galactosidase-labelled anti-human immunoglobulin conjugate (marketed by Cambridge Research Biochemicals) is added at a dilution of 1/200, and the mixture is incubated for two hours at room temperature. After washes of the membranes with 0.05% TBS-T and PBS, the immunoreactivity in the different spots is visualized by adding 5-bromo-4-chloro-3-indolyl β-D-galactopyranoside in potassium. The intensity of coloration of the spots is estimated qualitatively with a relative value from 0 to 5 as shown in the attached Figures 31 to 33.

In this way, it is possible to determine two immunodominant regions at each end of the POL2B peptide, corresponding, respectively, to the amino acid sequences 65-75 (SEQ ID NO:41) and 92-109 (SEQ ID NO:42), according to Figure 34, and lying, respectively, between the octapeptides Phe-Cys-Ile-Pro-Val-Arg-Pro-Asp (FCIPVRPD) and Arg-Pro-Asp-Ser-Gln-Phe-Leu-Phe (RPDSQFLF), and

Thr-Val-Leu-Pro-Gln-Gly-Phe-Arg (TVLPQGFR) and Leu-Phe-Gly-Gln-Ala-Leu-Ala-Gln (LFGQALAQ), and a region which is less reactive but apparently more specific, since it does not produce any background with the control serum, represented by the octapeptides Leu-Phe-Ala-Phe-Glu-Asp-Pro-Leu (LFAFEDPL) (SEQ ID NO:43) and Phe-Ala-Phe-Glu-Asp-Pro-Leu-Asn (FAFEDPLN) (SEQ ID NO:44).

These regions make it possible to define new peptides which are more specific and more immunoreactive according to the usual techniques.

It is thus possible, as a result of the discoveries made and the methods developed by the inventors, to carry out a diagnosis of MSRV-1 infection and/or reactivation and to evaluate a therapy in MS on the basis of its efficacy in "negativing" the detection of these agents in the patients' biological fluids. Furthermore, early detection in individuals not yet displaying neurological signs of MS could make it possible to institute a treatment which would be all the more effective with respect to the subsequent clinical course for the fact that it would precede the lesion stage which corresponds to the onset of neurological disorders. Now, at the present time, a diagnosis of MS cannot be established before a symptomatology of neurological lesions has set in, and hence no treatment is instituted before the emergence of a clinical picture suggestive of lesions of the central nervous system which are already significant. The diagnosis of an MSRV-1 and/or MSRV-2 infection and/or reactivation in man is hence of decisive importance, and the present invention provides the means of doing this.

It is thus possible, apart from carrying out a diagnosis of MSRV-1 infection and/or reactivation, to evaluate a therapy in MS on the basis of its efficacy in "negativing" the detection of these agents in the patients' biological fluids.

EXAMPLE 12: OBTAINING A CLONE LB19 CONTAINING A PORTION OF THE gag GENE OF THE MSRV-1 RETROVIRUS

A PCR technique derived from the technique published by Gonzalez-Quintial R et al. (19) and PLAZA et al. (25) was used. From the total RNAs extracted from a fraction of virion purified as described above, the cDNA was synthesized using a specific primer (SEQ ID No.64) at the 3' end of the genome to be amplified, using EXPAND™ REVERSE TRANSCRIPTASE (BOEHRINGER MANNHEIM).

cDNA:
AAGGGGCATG GACGAGGTGG TGGCTTATTT (SEQ ID NO:65) (antisense)

After purification, a poly(G) tail was added at the 5' end of the cDNA using the "Terminal transferases kit" marketed by the company Boehringer Mannheim, according to the manufacturer's protocol.

An anchoring PCR was carried out using the following 5' and 3' primers:
AGATCTGCAG AATTCGATAT CACCCCCCCC CCCCCC (SEQ ID No. 91) (sense), and AAATGTCTGC GGCACCAATC TCCATGTT (SEQ ID No. 64) (antisense)

Next, a semi-nested anchoring PCR was carried out with the following 5' and 3' primers:
AGATCTGCAG AATTCGATAT CA (SEQ ID No.92) (sense), and AAATGTCTGC GGCACCAATC TCCATGTT (SEQ ID No.64) (antisense)

The products originating from the PCR were purified after purification on agarose gel according to conventional methods (17), and then resuspended in 10 microlitres of distilled water. Since one of the properties of Taq polymerase consists in adding an adenine at the 3' end of each of the two DNA strands, the DNA obtained was inserted directly into a plasmid using the TA Cloning™ kit (British Biotechnology). The 2 μl of DNA solution were mixed with 5 μl of sterile distilled water,

1 μl of 10-fold concentrated ligation buffer "10x LIGATION BUFFER", 2 μl of "pCR™ VECTOR" (25 ng/ml) and 1 μl of "T4 DNA LIGASE". This mixture was incubated overnight at 12°C. The following steps were carried out according to the instructions of the TA Cloning™ kit (British Biotechnology). At the end of the procedure, the white colonies of recombinant bacteria (white) were picked out in order to be cultured and to permit extraction of the plasmids incorporated according to the so-called "miniprep" procedure (17). The plasmid preparation from each recombinant colony was cut with a suitable restriction enzyme and analysed on agarose gel. Plasmids possessing an insert detected under UV light after staining the gel with ethidium bromide were selected for sequencing of the insert, after hybridization with a primer complementary to the Sp6 promoter present on the cloning plasmid of the TA Cloning Kit™. The reaction prior to sequencing was then performed according to the method recommended for the use of the sequencing kit "Prism ready reaction kit dye deoxyterminator cycle sequencing kit" (Applied Biosystems, ref. 401384), and automatic sequencing was carried out with an Applied Biosystems "Automatic Sequencer, model 373 A" apparatus according to the manufacturer's instructions.

PCR amplification according to the technique mentioned above was used on a cDNA synthesized from the nucleic acids of fractions of infective particles purified on a sucrose gradient, according to the technique described by H. Perron (13), from culture supernatants of B lymphocytes of a patient suffering from MS, immortalized with Epstein-Barr virus (EBV) strain B95 and expressing retroviral particles associated with reverse transcriptase activity as described by Perron et al. (3) and in French Patent Applications MS 10, 11 and 12. the clone LB19, whose sequence, identified by SEQ ID NO:59, is presented in Figure 35.

The clone makes it possible to define, with the clone GM3 previously sequenced and the clone G+E+A (see Example 15), a region of 690 base pairs representative of a significant portion of the gag gene of the MSRV-1 retrovirus, as presented in Figure 36. This sequence designated SEQ ID NO:88 is reconstituted from different clones overlapping at their ends. This sequence is identified under the name MSRV-1 "gag*" region. In Figure 36, a potential reading frame with the translation into amino acids is presented below the nucleic acid sequence.

EXAMPLE 13: OBTAINING A CLONE FBd13 CONTAINING A pol GENE REGION RELATED TO THE MSRV-1 RETROVIRUS AND AN APPARENTLY INCOMPLETE ENV REGION CONTAINING A POTENTIAL READING FRAME (ORF) FOR A GLYCOPROTEIN

Extraction of viral RNAs: The RNAs were extracted according to the method briefly described below.

A pool of culture supernatant of B lymphocytes of patients suffering from MS (650 ml) is centrifuged for 30 minutes at 10,000 g. The viral pellet obtained is resuspended in 300 microlitres of PBS/10 mM $MgCl_2$. The material is treated with a DNAse (100 mg/ml)/RNAse (50 mg/ml) mixture for 30 minutes at 37°C and then with proteinase K (50 mg/ml) for 30 minutes at 46°C.

The nucleic acids are extracted with one volume of a phenol/0.1% SDS (V/V) mixture heated to 60°C, and then re-extracted with one volume of phenol/chloroform (1:1; V/V).

Precipitation of the material is performed with 2.5 V of ethanol in the presence of 0.1 V of sodium acetate pH5.2. The pellet obtained after centrifugation is resuspended in 50 microlitres of sterile DEPC water.

The sample is treated again with 50 mg/ml of "RNAse free" DNAse for 30 minutes at room temperature, extracted with one volume of phenol/chloroform and

precipitated in the presence of sodium acetate and ethanol.

The RNA obtained is quantified by an OD reading at 260 nm. The presence of MSRV-1 and the absence of DNA contaminant is monitored by a PCR and an MSRV-1-specific RTPCR associated with a specific ELOSA for the MSRV-1 genome.

Synthesis of cDNA:

5 mg of RNA are used to synthesize a cDNA primed with a poly(DT) oligonucleotide according to the instructions of the "cDNA Synthesis Module" kit (ref RPN 1256, Amersham) with a few modifications: The reverse transcription is performed at 45°C instead of the recommended 42°C.

The synthesis product is purified by a double extraction and a double purification according to the manufacturer's instructions.

The presence of MSRV-1 is verified by an MSRV-1 PCR associated with a specific ELOSA for the MSRV-1 genome.

"Long Distance PCR": (LD-PCR)

500 ng of cDNA are used for the LD-PCR step (Expand Long Template System; Boehringer (ref.1681 842)).

Several pairs of oligonucleotides were used. Among these, the pair defined by the following primers:

5' primer: GGAGAAGAGC AGCATAAGTG G (SEQ ID NO:66)

3' primer: GTGCTGATTG GTGTATTTAC AATCC (SEQ ID NO:67).

The amplification conditions are as follows:

94°C 10 seconds
56°C 30 seconds
68°C 5 minutes;

10 cycles, then 20 cycles with an increment of 20 seconds in each cycle on the elongation time. At the end of this first amplification, 2 microlitres of the amplification product are subjected to a second amplification under the same conditions as before.

The LD-PCR reactions are conducted in a Perkin model 9600 PCR apparatus in thin-walled microtubes (Boehringer).

The amplification products are monitored by electrophoresis of 1/5th of the amplification volume (10 microlitres) in 1% agarose gel. For the pair of primers described above, a band of approximately 1.7 Kb is obtained.

Cloning of the amplified fragment:

The PCR product was purified by passage through a preparative agarose gel and then through a Costar column (Spin; D. Dutcher) according to the supplier's instructions.

2 microlitres of the purified solution are joined up with 50 ng of vector PCRII according to the supplier's instructions (TA Cloning Kit; British Biotechnology)).

The recombinant vector obtained is isolated by transformation of competent DH5αF' bacteria. The bacteria are selected using their resistance to ampicillin and the loss of metabolism for Xgal (= white colonies). The molecular structure of the recombinant vector is confirmed by plasmid minipreparation and hydrolysis with the enzyme EcoR1.

FBd13, a positive clone for all these criteria, was selected. A large-scale preparation of the recombinant plasmid was performed using the Midiprep Quiagen kit (ref 12243) according to the supplier's instructions.

Sequencing of the clone FBd13 is performed by means of the Perkin Prism Ready Amplitaq FS dye terminator kit (ref. 402119) according to the manufacturer's instructiions. The sequence reactions are introduced into a Perkin type 377 or 373A automatic sequencer. The sequencing strategy consists in gene walking carried out on both strands of the clone Fbd13.

The sequence of the clone FBd13 is identified by SEQ ID NO:58.

In Figure 37, the sequence homology between the clone FBd13 and the HSERV-9 retrovirus is shown on the matrix chart by a continuous line for any partial homology greater than or equal to 70%. It can be seen that there are homologies in the flanking regions of the clone (with the pol gene at the 5' end and with the env gene and then the LTR at the 3' end), but that the internal region is totally divergent and does not display any homology, even weak, with the env gene of HSERV-9. Furthermore, it is apparent that the clone FBd13 contains a longer "env" region than the one which is described for the defective endogenous HSERV-9; it may thus be seen that the internal divergent region constitutes an "insert" between the regions of partial homology with the HSERV-9 defective genes.

This additional sequence determines a potential orf, designated ORF B13, which is represented by its amino acid sequence SEQ ID NO:87.

The molecular structure of the clone FBd13 was analyzed using the GeneWork software and Genebank and SwissProt data banks.

5 glycosylation sites were found.

The protein does not have significant homology with already known sequences.

It is probable that this clone originates from a recombination of an endogenous retroviral element (ERV), linked to the replication of MSRV-1.

Such a phenomenon does not lack generation of the expression of polypeptides, or even of endogenous retroviral proteins which are not necessarily tolerated by the immune system. Such a scheme of aberrant expression of endogenous elements related to MSRV-1 and/or induced by the latter is liable to multiply the aberrant antigens, and hence tends to contribute to the induction of

autoimmune processes such as are observed in MS. It clearly constitutes a novel element never hitherto described. In effect, interrogation of the data banks of nucleic acid sequences available in version No. 19 (1996) of the "Entrez" software (NCBI, NIH, Bethesda, USA) did not enable a known homologous sequence comprising the whole of the env region of this clone to be identified.

EXAMPLE 14: OBTAINING A CLONE FP6 CONTAINING A PORTION OF THE pol GENE, WITH A REGION CODING FOR THE REVERSE TRANSCRIPTASE ENZYME HOMOLOGOUS TO THE CLONE POL* MSRV-1, AND A 3'pol REGION DIVERGENT FROM THE EQUIVALENT SEQUENCES DESCRIBED IN THE CLONES POL*, tpol, FBd3, JLBc1 and JLBc2

A 3'RACE was performed on total RNA extracted from plasma of a patient suffering from MS. A healthy control plasma treated under the same conditions was used as negative control. The synthesis of cDNA was carried out with the following modified oligo(dT) primer:

5' GACTCGCTGC AGATCGATTT TTTTTTTTTT TTTT 3' (SEQ ID NO:68)

and Boehringer "Expand RT" reverse transcriptase according to the conditions recommended by the company. A PCR was performed with the enzyme Klentaq (Clontech) under the following conditions: 94°C 5 min then 93°C 1 min, 58°C 1 min, 68°C 3 min for 40 cycles and 68°C for 8 min, and with a final reaction volume of 50 μl.

Primers used for the PCR:

- 5' primer, identified by SEQ ID NO:69

5' GCCATCAAGC CACCCAAGAA CTCTTAACTT 3';

- 3' primer, identified by SEQ ID NO:68 (=the same as for the cDNA)

A second, so-called "semi-nested" PCR was carried out with a 5' primer located within the region already amplified. This second PCR was performed under the same experimental conditions as those used in the first

PCR, using 10 μl of the amplification product originating from the first PCR.

Primers used for the semi-nested PCR:

- 5' primer, identified by SEQ ID NO:70

5' CCAATAGCCA GACCATTATA TACACTAATT 3';

- 3' primer, identified by SEQ ID NO:68 (=the same as for the cDNa)

Primers SEQ ID NO:69 and SEQ ID NO:70 are specific for the pol* region: position No. 403 to No. 422 and No. 641 to No. 670, respectively.

An amplification product was thus obtained from the extracellular RNA extracted from the plasma of a patient suffering from MS. The corresponding fragment was not observed for the plasma of the healthy control. This amplification product was cloned in the following manner.

The amplified DNA was inserted into a plasmid using the TA Cloning™ kit. The 2 μl of DNA solution were mixed with 5 μl of sterile distilled water, 1 μl of a 10-fold concentrated ligation buffer "10x LIGATION BUFFER", 2 μl of "pCR™ VECTOR" (25 ng/ml) and 1 μl of "TA DNA LIGASE". This mixture was incubated overnight at 12°C. The following steps were carried out according to the instructions of the TA Cloning™ kit (British Biotechnology). At the end of the procedure, the white columns of recombinant bacteria (white) were picked out in order to be cultured and to permit extraction of the plasmids incorporated according to the so-called "miniprep" procedure (17). The plasmid preparation from each recombinant colony was cut with a suitable restriction enzyme and analyzed on agarose gel. Plasmids possessing an insert detected under UV light after staining the gel with ethidium bromide was selected for sequencing of the insert, after hybridization with a primer complementary to the Sp6 promoter present on the cloning plasmid of the TA cloning kit™. The reaction prior to sequencing was then performed according to the method

recommended for the use of the sequencing kit "Prism ready reaction kit dye deoxyterminator cycle sequencing kit" (Applied Biosystems, ref. 401384), and automatic sequencing was carried out with an Applied Biosystems "Automatic Sequencer, model 373 A" apparatus according to the manufacturer's instructions.

The clone obtained, designated FP6, enables a region of 467 bp which is 89% homologous to the pol* region of the MSRV-1 retrovirus and a region of 1167 bp which is 64% homologous to the pol region of ERV-9 (No. 1634 to 2856) to be defined.

The clone FP6 is represented in Figure 38 by its nucleotide sequence identified by SEQ ID NO:61. The three potential reading frames of this clone are indicated by their amino acid sequence under the nucleotide sequence.

EXAMPLE 15: OBTAINING A REGION DESIGNATED G+E+A CONTAINING AN ORF FOR A RETROVIRAL PROTEASE, BY PCR AMPLIFICATION OF THE NUCLEIC ACID SEQUENCE CONTAINED BETWEEN THE 5' REGION DEFINED BY THE CLONE "GM3" AND THE 3' REGION DEFINED BY THE CLONE POL*, FROM THE RNA EXTRACTED FROM A POOL OF PLASMAS OF PATIENTS SUFFERING FROM MS

Oligonucleotides specific for the MSRV-1 sequences already identified by the Applicant were defined in order to amplify the retroviral RNA originating from virions present in the plasma of patients suffering from MS. Control reactions were performed so as to monitor the presence of contaminants (reaction with water). The amplification consists of a step of RT-PCR followed by a "nested" PCR. Pairs of primers were defined for amplifying three overlapping regions (designated G, E and A) on the regions defined by the sequences of the clones GM3 and pol* described above.

Semi-nested RT-PCR for amplification of the region G:

- in the first RT-PCR cycle, the following primers are used:

primer 1: SEQ ID NO:71 (sense)
primer 2: SEQ ID NO:72 (antisense)

- in the second PCR cycle, the following primers are used:

primer 1: SEQ ID NO:73 (sense)
primer 4: SEQ ID NO:74 (antisense)

Nested RT-PCR for amplification of the region E:

- in the first RT-PCR cycle, the following primers are used:

primer 5: SEQ ID NO:75 (sense)
primer 6: SEQ ID NO:76 (antisense)

- in the second PCR cycle, the following primers are used:

primer 7: SEQ ID NO:77 (sense)
primer 8: SEQ ID NO:78 (antisense)

Semi-nested RT-PCR for amplification of the region A:

- in the first RT-PCR cycle, the following primers are used:

primer 9: SEQ ID NO:79 (sense)
primer 10: SEQ ID NO:80 (antisense)

- in the second PCR cycle, the following primers are used:

primer 9: SEQ ID NO:81 (sense)
primer 11: SEQ ID NO:82 (antisense)

The primers and the regions G, E and A which they define are positioned as follows:

cDNA

```
          1_____G_____4  2
                5  7______E______________8  6
                                         3_____A_____11  10
<------------------------><-------------------------->
          GM3                            POL*
```

The sequence of the region defined by the different clones G, E and A was determined after cloning and sequencing of the "nested" amplification products.

The clones G, E and A were assembled together by PCR with the primers 1 at the 5' end of the fragment G and 11 at the 3' end of the fragment A, the primers being described above. An approximately 1580-bp fragment G+E+A was amplified and inserted into a plasmid using the TA Cloning (trademark) kit. The sequence of the amplification product corresponding to G+E+A was determined and analysis of the G+E and E+A overlaps was carried out. The sequence is shown in Figure 39, and corresponds to the sequence SEQ ID NO:89.

A reading frame coding for an MSRV-1 retroviral protease was found in the region E. The amino acid sequence of the protease, identified by SEQ ID NO:90, is presented in Figure 40.

EXAMPLE 16: OBTAINING A CLONE LTRGAG12, RELATED TO AN ENDOGENOUS RETROVIRAL ELEMENT (ERV) CLOSE TO MSRV-1, IN THE DNA OF AN MS LYMPHOBLASTOID LINE PRODUCING VIRIONS AND EXPRESSING THE MSRV-1 RETROVIRUS

A nested PCR was performed on the DNA extracted from a lymphoblastoid line (B lymphocytes immortalized with the EBV virus strain B95, as described above and as is well known to a person skilled in the art) expressing the MSRV-1 retrovirus and originating from peripheral blood lymphocytes of a patient suffering from MS.

In the first PCR step, the following primers are used:

primer 4327: CTCGATTTCT TGCTGGGCCT TA (SEQ ID NO:83)

primer 3512: GTTGATTCCC TCCTCAAGCA (SEQ ID NO:84)

This step comprises 35 amplification cycles with the following conditions: 1 min at 94°C, 1 min at 54°C and 4 min at 72°C.

In the second PCR step, the following primers are used:

primer 4294: CTCTACCAAT CAGCATGTGG (SEQ ID NO:85)

primer 3591: TGTTCCTCTT GGTCCCTAT (SEQ ID NO:86)

This step comprises 35 amplification cycles with the following conditions: 1 min at 94°C, 1 min at 54°C and 4 min at 72°C.

The products originating from the PCR were purified after purification on agarose gel according to conventional methods (17), and then resuspended in 10 ml of distilled water. Since one of the properties of Taq polymerase consists in adding an adenine at the 3' end of each of the two DNA strands, the DNA obtained was inserted directly into a plasmid using the TA Cloning™ kit (British Biotechnology). The 2 μl of DNA solution were mixed with 5 μl of sterile distilled water, 1 μl of a 10-fold concentrated ligation buffer "10x LIGATION BUFFER", 2 μl of "pCR™ VECTOR" (25 ng/ml) and 1 μl of "TA DNA LIGASE". This mixture was incubated overnight at 12°C. The following steps were carried out according to the instructions of the TA Cloning™ kit (British Biotechnology). At the end of the procedure, the white colonies of recombinant bacteria (white) were picked out in order to be cultured and to permit extraction of the plasmids incorporated according to the so-called "miniprep" procedure (17). The plasmid preparation from each recombinant colony was cut with a suitable restriction enzyme and analyzed on agarose gel. The plasmids possessing an insert detected under UV light after staining the gel with ethidium bromide were selected for sequencing of the insert, after hybridization with a primer complementary to the Sp6 promoter present on the cloning plasmid of the TA Cloning Kit™. The reaction prior to sequencing was then performed according to the method recommended for the use of the sequencing kit "Prism ready reaction kit dye deoxyterminator cycle sequencing kit"

(Applied Biosystems, ref. 401384), and automatic sequencing was carried out with an Applied Biosystems "Automatic Sequencer, model 373 A" apparatus according to the manufacturer's instructions.

Thus, a clone designated LTRGAG12 could be obtained, and is represented by its internal sequence identified by SEQ ID NO:60.

This clone is probably representative of endogenous elements close to ERV-9, present in human DNA, in particular in the DNA of patients suffering from MS, and capable of interfering with the expression of the MSRV-1 retrovirus, hence capable of having a role in the pathogenesis associated with the MSRV-1 retrovirus and capable of serving as marker for a specific expression in the pathology in question.

EXAMPLE 17: DETECTION OF ANTI-MSRV-1 SPECIFIC ANTIBODIES IN HUMAN SERUM

Identification of the sequence of the pol gene of the MSRV-1 retrovirus and of an open reading frame of this gene enabled the amino acid sequence SEQ ID NO:63 of a region of the said gene, referenced SEQ ID NO:62, to be determined.

Different synthetic peptides corresponding to fragments of the protein sequence of MSRV-1 reverse transcriptase encoded by the pol gene were tested for their antigenic specificity with respect to sera of patients suffering from MS and of healthy controls.

The peptides were synthesized chemically by solid-phase synthesis according to the Merrifield technique (22). The practical details are those described below.

a) Peptide synthesis:

The peptides were synthesized on a phenylacetamidomethyl (PAM)/polystyrene/divinylbenzene resin (Applied Biosystems, Inc. Foster City, CA), using an

"Applied Biosystems 430A" automatic synthesizer. The amino acids are coupled in the form of hydroxybenzotriazole (HOBT) esters. The amino acids used are obtained from Novabiochem (Läuflerlfingen, Switzerland) or Bachem (Bubendorf, Switzerland).

The chemical synthesis was performed using a double coupling protocol with N-methylpyrrolidone (NMP) as solvent. The peptides were cut from the resin, as well as the side-chain protective groups, simultaneously, using hydrofluoric acid (HF) in a suitable apparatus (type I cleavage apparatus, Peptide Instiute, Osaka, Japan).

For 1 g of peptidyl resin, 10 ml of HF, 1 ml of anisole and 1 ml of dimethyl sulphide 5DMS are used. The mixture is stirred for 45 minutes at -2°C. The HF is then evaporated off under vacuum. After intensive washes with ether, the peptide is eluted from the resin with 10% acetic acid and then lyophilized.

The peptides are purified by preparative high performance liquid chromatography on a VYDAC C18 type column (250 x 21 mm) (The Separation Group, Hesperia, CA, USA). Elution is carried out with an acetonitrile gradient at a flow rate of 22 ml/min. The fractions collected are monitored by an elution under isocratic conditions on a VYDAC™ C18 analytical column (250 x 4.6 mm) at a flow rate of 1 ml/min. Fractions having the same retention time are pooled and lyophilized. The preponderant fraction is then analysed by analytical high performance liquid chromatography with the system described above. The peptide which is considered to be of acceptable purity manifests itself in a single peak representing not less than 95% of the chromatogram.

The purified peptides are then analysed with the object of monitoring their amino acid composition, using an Applied Biosystems 420H automatic amino acid analyser. Measurement of the (average) chemical molecular mass of the peptides is obtained using LSIMS mass spectrometry in

the positive ion mode on a VG. ZAB.ZSEQ double focusing instrument connected to a DEC-VAX 2000 acquisition system (VG analytical Ltd, Manchester, England).

The reactivity of the different peptides was tested against sera of patients suffering from MS and against sera of healthy controls. This enabled a peptide designated S24Q to be selected, whose sequence is identified by SEQ ID NO:63, encoded by a nucleotide sequence of the pol gene of MSRV-1 (SEQ ID NO:62).

b) Antigenic properties:

The antigenic properties of the S24Q peptide were demonstrated according to the ELISA protocol described below.

The lyophilized S24Q peptide was dissolved in 10 % acetic acid at a concentration of 1 mg/ml. This stock solution was aliquoted and kept at +4°C for use over a fortnight, or frozen at -20°C for use within 2 months. An aliquot is diluted in PBS (phosphate buffered saline) solution so as to obtain a final peptide concentration of 5 micrograms/ml. 100 microlitres of this dilution are placed in each well of Nunc Maxisorb (trade name) microtitration plates. The plates are covered with a "plate-sealer" type adhesive and kept for 2 hours at +37°C for the phase of adsorption of the peptide to the plastic. The adhesive is removed and the plates are washed three times with a volume of 300 microlitres of a solution A (1X´ PBS, 0.05% Tween 20®), then inverted over an absorbent tissue. The plates thus drained are filled with 250 microlitres per well of a solution B (solution A + 10% of goat serum), then covered with an adhesive and incubated for 1 hour at 37°C. The plates are then washed three times with the solution A as described above.

The test serum samples are diluted beforehand to 1/100 in the solution B, and 100 microlitres of each dilute test serum are placed in the wells of each micro-

titration plate. A negative control is placed in one well of each plate, in the form of 100 microlitres of buffer B. The plates covered with an adhesive are then incubated for 1 hour 30 min at 37°C. The plates are then washed three times with the solution A as described above. For the IgG response, a peroxidase-labelled goat antibody directed against human IgG (marketed by Jackson Immuno Research Inc.) is diluted in the solution B (dilution 1/10,000). 100 microlitres of the appropriate dilution of the labelled antibody are then placed in each well of the microtitration plates, and the plates covered with an adhesive are incubated for 1 hour at 37°C. A further washing of the plates is then performed as described above. In parallel, the peroxidase substrate is prepared according to the directions of the bioMérieux kits. 100 microlitres of substrate solution are placed in each well, and the plates are placed protected from light for 20 to 30 minutes at room temperature.

When the colour reaction has stabilized, 50 microlitres of Color 2 (bioMérieux trade name) are placed in each well in order to stop the reaction. The plates are placed immediately in an ELISA plate spectrophotometric reader, and the optical density (OD) of each well is read at a wavelength of 492 nm.

The serological samples are introduced in duplicate or in triplicate, and the optical density (OD) corresponding to the serum tested is calculated by taking the mean of the OD values obtained for the same sample at the same dilution.

The net OD of each serum corresponds to the mean OD of the serum minus the mean OD of the negative control (solution B: PBS, 0.05% Tween 20x, 10% goat serum).

c) Detection of anti-MSRV-1 IgG antibodies (S24Q) by ELISA:

The technique described above was used with the S24Q peptide to test for the presence of anti-MSRV-1

specific IgG antibodies in the serum of 15 patients for whom a definite diagnosis of MS was established according to the criteria of Poser (23), and of 15 healthy controls (blood donors).

Figure 41 shows the results for each serum tested with an anti-IgG antibody. Each vertical bar represents the net optical density (OD at 492 nm) of a serum tested. The ordinate axis gives the net OD at the top of the vertical bars. The first 15 vertical bars lying to the left of the vertical broken line represent the sera of 15 healthy controls (blood donors), and the 15 vertical bars lying to the right of the vertical broken line represent the sera of 15 cases of MS tested. The diagram enables 2 controls to be revealed whose OD rises above the grouped values of the control population. These values may represent the presence of specific IgGs in symptomless seropositive patients. Two methods were hence evaluated in order to determine the statistical threshold of positivity of the test.

The mean of the net OD values for the controls, including the controls with high net OD values, is 0.129 and the standard deviation is 0.06. Without the 2 controls whose OD values are greater than 0.2, the mean of the "negative" controls is 0.107 and the standard deviation is 0.03. A theoretical threshold of positivity may be calculated according to the formula:

threshold value (mean of the net OD values of the negative controls) + (2 or 3 ´ standard deviation of the net OD values of the negative controls).

In the first case, there are considered to be symptomless seropositives, and the threshold value is equal to 0.11 + (3 x 0.03) = 0.20. The negative results represent a non-specific "background" of the presence of

antibodies directed specifically against an epitope of the peptide.

In the second case, if the set of controls consisting of blood donors in apparent good health is taken as a reference basis, without excluding the sera which are, on the face of it, seropositive, the standard deviation of the "non-MS controls" is 0.116. The threshold value then becomes 0.13 + (3 x 0.06) = 0.31.

According to this latter analysis, the test is specific for MS. In this respect, it is seen that the test is specific for MS, since, as shown in Table 1, no control has a net OD above this threshold. In fact, this result reflects the fact that the antibody titres in patients suffering from MS are, for the most part, higher than in healthy controls who have been in contact with MSRV-1.

In accordance with the first method of calculation, and as shown in Figure 41 and in Table 3, 6 of the 15 MS sera give a positive result (OD greater than or equal to 0.2), indicating the presence of IgGs specifically directed against the S24Q peptide, hence against a portion of the reverse transcriptase enzyme of the MSRV-1 retrovirus encoded by its pol gene, and consequently against the MSRV-1 retrovirus.

Thus, approximately 40% of the MS patients tested have reacted against an epitope carried by the S24Q peptide and possess circulating IgGs directed against the latter.

Two out of 15 blood donors in apparent good health show a positive result. Thus, it is apparent that approximately 13% of the symptomless population may have been in contact with an epitope carried by the S24Q peptide under conditions which have led to an active immunization which manifests itself in the persistence of specific serum IgGs. These conditions are compatible with an immunization against the MSRV-1 retrovirus reverse transcriptase during an infection with (and/or reactiva-

tion of) the MSRV-1 retrovirus. The absence of apparent neurological pathology recalling MS in these seropositive controls may indicate that they are healthy carriers and have eliminated an infectious virus after immunizing themselves, or that they constitute an at-risk population of chronic carriers. In effect, epidemiological data showing that a pathogenic agent present in the environment of regions of high prevalence of MS may be the cause of this disease imply that a fraction of the population free from MS has necessarily been in contact with such a pathogenic agent. It has been shown that the MSRV-1 retrovirus constitutes all or part of this "pathogenic agent" at the source of MS, and it is hence normal for controls taken from a healthy population to possess IgG type antibodies against components of the MSRV-1 retrovirus.

Lastly, the detection of anti-S24Q antibodies in only one out of two MS cases tested here may reflect the fact that this peptide does not represent an immunodominant MSRV-1 epitope, that inter-individual strain variations may induce an immunization against a divergent peptide motif in the same region, or that the course of the disease and the treatments followed may modulate over time the antibody response against the S24Q peptide.

TABLE No. 3

	CONTROLS	MS
	0.101	0.136
	0.058	0.391
	0.126	0.37
	0.131	0.119
	0.105	0.267
	0.294	0.141
	0.116	0.102
	0.088	0.18
	0.1 05	0.411
	0.172	0.164
	0.137	0.049
	0.223	0.644
	0.08	0.268
	0.073	0.065
	0.132	0.074
Mean	0.129	
Std. Dev.	0.06	
Threshold	0.31	

d) Detection of anti-MSRV-1 IgM antibodies by ELISA:

The ELISA technique with the S24Q peptide was used to test for the presence of anti-MSRV-1 IgM specific antibodies in the same sera as above.

Figure 42 shows the results for each serum tested with an anti-IgM antibody. Each vertical bar represents the net optical density (OD at 492 nm) of a serum tested. The ordinate axis gives the net OD at the top of the vertical bars. The first 15 vertical bars lying to the left of the vertical line cutting the abscissa axis represent the sera of 15 healthy controls (blood donors), and the vertical bars lying to the right of the vertical broken line represent the sera of 15 cases of MS tested.

The mean of the OD values for the MS cases tested is 1.6.

The mean of the net OD values for the controls is 0.7.

The standard deviation of the negative controls is 0.6.

The threshold of theoretical positivity may be calculated according to the formula:

threshold value = (mean of the OD values of the negative controls) + (3 x standard deviation of the OD values of the negative controls)

The threshold value is hence equal to 0.7 + (3 x 0.6) = 2.5;

The negative results represent a non-specific "background" of the presence of antibodies directed specifically against an epitope of the peptide.

According to this analysis, and as shown in Figure 42 and in the corresponding Table 4, the IgM test is specific for MS, since no control has a net OD above the threshold. 6 of the 15 MS sera produce a positive IgM result

The difference in seroprevalence between the MS and control populations is extremely significant: "chi-squared" test, $p < 0.002$.

These results point to an aetiopathogenic role of MSRV-1 in MS.

Thus, the detection of IgM and IgG antibodies against the S24Q peptide makes it possible to evaluate, alone or in combination with other MSRV-1 peptides, the course of an MSRV-1 infection and/or of the viral reactivation of MSRV-1.

TABLE No. 4

	CONTROLS	MS
	1.449	0.974
	0.371	6.117
	0.448	2.883
	0.456	1.945
	0.885	1.787
	2.235	0.273
	0.301	1.766
	0.138	0.668
	0.16	2.603
	1.073	0.802
	1.366	0.245
	0.283	0.147
	0.262	2.441
	0.585	0.287
	0.356	0.589
Mean	0.7	
Std. Dev.	0.6	
Threshold Value	2.5	

It is possible, as a result of the new discoveries made and the new methods developed by the inventors, to permit the improved implementation of diagnostic tests for MSRV-1 infection and/or reactivation and to evaluate a therapy in MS and/or RA on the basis of its efficacy in "negativing" the detection of these agents in the patient's biological fluids. Furthermore, early detection in individuals not yet displaying neurological signs of MS or rheumatological signs of RA could make it possible to institute a treatment which would be all the more effective with respect to the subsequent clinical course for the fact that it would precede the lesion stage which corresponds to the onset of the clinical disorders. Now, at the present time, a diagnosis of MS or RA cannot be established before a symptomatology of lesions has set in, and hence no treatment is instituted before the emergence of a clinical picture suggestive of lesions which are already significant. The diagnosis of an MSRV-1 and/or MSRV-2 infection and/or reactivation in man is

hence of decisive importance, and the present invention provides the means of doing this.

It is thus possible, apart from carrying out a diagnosis of MSRV-1 infection and/or reactivation, to evaluate a therapy in MS on the basis of its efficacy in "negativing" the detection of these agents in the patients' biological fluids.

EXAMPLE 18 :

1) MATERIALS AND METHODS

- Patients and clinical samples

Choroid plexus cells from MS patients and controls were obtained from the brain-cell library, Laboratoire R. Escourolles, Hôpital de la Salpêtriére, Paris, France. Non-tumoral leptomeningeal cells from controls were obtained as previously described (26). Peripheral blood from MS and control patients used for obtaining B-cell lines and plasma, were obtained from the Neurological Departments, CHU de Grenoble, and from INSERM U 134, Hôpital de la Salpêtriére, France. Clinical details and origin of the 10 MS patients and of the 10 patients with other neurological diseases who provided CSF samples are given in Table 6.

- Cell cultures, virus isolation and purification

All cell-types were cultured as previously described (3, 5, 26).

All cultures were regularly screened for mycoplasma contamination with an ELISA mycoplasma-detection kit (Boehringer). No cell-extract nor supernatant used contained detectable mycoplasma.

Extracellular virion purification and sucrose density gradients were performed as previously described (3, 5, 26). From each sucrose gradient 0.5-1ml fractions were collected from the top of the tubes, with a 1000µl Pipetman and a different sterile tip for each fraction. 60µl were used for RT activity assay and the rest was

mixed with 1 volume of buffer containing 4M guanidinium thiocyanate, 0.5% N-Lauroyl sarcosin, 25mM EDTA, 0.2% ß-mercaptoethanol adjusted at pH 5.5 with acetic acid. These mixtures were frozen at -80°C for futher RNA extraction or directly processed according to Chomzynski (20), with an overnight precipitation step at -20°C, in presence of RNase-free glycogen (Boehringer). RNA was dissolved 20 to 50µl of DEPC-treated water in the presence of 1-2µl of recombinant RNase-inhibitor (PROMEGA) and 0,1mM DTT. 10µl aliquots were used for each RT-PCR.

- Reverse transcriptase activity

RT-activity was tested with 20mM Mg^{++} and poly-Cm or polyC templates, in virion pellets or fractions from sucrose gradients as previously described (3, 5, 26).

- cDNA synthesis and 'Pan-retro' RT-PCR with degenerate primers

A total RT-activity between 10^6-10^7 dpm was required in the fraction containing the peak of purified virions. The "Pan-retro" RT-PCR technique (27) was performed on virion RNA extracted by the method of Chomczynski (20) and dissolved in 20 µl RNase-free water. 5 µl RNA solution was incubated for 30 min at 37°C with 0.3 units (3 units for CSF series) of RNase-free DNase-1 (Boehringer) in a 20 µl reaction containing 7.5 mM random hexamers, 5 mM Hepes-HCl pH 6.9, 75 mM KCl, 3 mM $MgCl_2$, 10 mM DTT, 50 mM Tris-HCl pH 7.5, 0.5 mM each dNTP, and 20 units recombinant RNase inhibitor (Promega). The DNase was then heat inactivated at 80°C for 10 min. 20 units MoMLV RT (Pharmacia) and a further 20 units of RNase inhibitor were added to each tube in a Genesphere™ enclosure (Safetech, Ireland) and cDNA was synthesised for 90 min at 37°C. Following reverse transcription, the cDNA was boiled for 5 min then cooled rapidly on ice. The Round 1 PCR mix (final volume 25 µl per reaction; 20 mM Tris-HCl pH 8.4, 60 mM KCl, 2.5 mM $MgCl_2$, 200 ng each of primers PAN-UO and PAN-DI [see Figure 44], 0.2 mM each dNTP) was treated with

0.3 units DNase-1 and then heat inactivated as above. 2.5 μl cDNA was added in the Genesphere™ enclosure and the tubes heated to 80°C before adding 0.5 units *Taq* polymerase (Perkin Elmer) individually to each tube ("hot start"). Round 1 PCR parameters were 35 cycles of 95°C for 1 min, 34°C for 30 sec, 72°C for 1 min, with a final 7 min extension at 72°C. 0.5 μl of Round 1 PCR product was transferred to the Round 2 DNase-treated PCR mix (composition as for Round 1 but containing primers PAN-UI and PAN-DI) using the "hot start" procedure. Round 2 PCR parameters were as for Round 1 but using 30 cycles only and annealing at 45°C for 1 min.

- Cloning of PCR products

PCR products were cloned using the TA-cloning® kit (British Biotechnology) according to the manufacturer's recommendations.

- Sequencing

Sequencing reactions were performed using the "Prism ready reaction kit dye deoxyterminator cycle sequencing kit" (Applied Biosystems). Automatic sequence analysis was performed on an automatic sequencer (Applied Biosystems, 373 A).

- RT-PCR with ST1 primer sets

The first PCR round was performed directly from the cDNA reaction mixture according to the one-step RT-PCR technique described by Mallet et al. (28). This one-step RT-PCR procedure reduced the probability of airborne contamination when opening the tubes and transferring PCR reagents after an independent cDNA synthesis. RNA was extracted as previously from 2ml of plasma (snap-frozen in liquid nitrogen and stored at -80°C) or from a 500 μl sucrose fraction with a total RT-activity above 10^6 dpm, and resuspended in 50 μl of RNase-free water. For each RT-PCR reaction 10μl of RNA solution was incubated in a Perkin-Elmer 480 thermocycler, 15 min at 20°C with 1U of RNase-free DNASE 1 and 1.2 μl of 10X DNASE buffer (50mM

Tris, 10mM MgCl2 and 0,1mM DTT) containing 1U/μl of RNase-inhibitor (PROMEGA), and heated at 70°C for 10 min for DNase inactivation. The solution was placed on ice and mixed (in conditions preventing airborne dust/DNA contamination) with 88 μl of PCR mix containing: 1X taq buffer, 25 nM/tube dNTPs, 40pM/tube of each first round primer (ST1.1 upstream primer: 5' AGGAGTAAGGAAACCCAACGGAC 3' (SEQ ID NO:99); ST1.1 downstream primer: 5'TAAGAGTTGCACAAGTGCG 3' (SEQ ID NO:100)), 2.5U/tube of taq (Appligene) and 10U/tube of AMV-RT (Boehringer). Each tube iwas further incubated in a Perkin-Elmer 480 thermocycler for 10 min at 65°C, followed by 2h at 42°C for cDNA synthesis and 5 min at 95°C for inactivation of AMV-RT and DNA denaturation. First round parameters were 40 cycles of 95°C for 1 min, 53°C for 2.5 min, 72°C for 1 min, with a final extension of 10 min at 72°C. 10μl of the first round were transferred to the second round PCR mix previously treated at 20°C for 15 min with RNase-free DNase 1 (0.02U/μl) followed by DNase inactivation at 70°C for 10 min. This mix contained 1X taq buffer, 25 nM/tube dNTPs, 40pM/tube of each second round primers [ST1.2 upstream primer: 5'TCAGGGATAGCCCCCATCTAT3' (SEQ ID NO:101); ST1.2 downstream primer: 5'AACCCTTTGCCACTACATCAATTT3' (SEQ ID NO:102)] and 2.5U/tube of taq (Appligene). Second round parameters were 30 cycles of 95°C for 1 min, 53°C for 1.5 min, 72°C for 1 min, with a final extension of 8 min at 72°C. 20μl of this nested RT-PCR product were deposited on a 0,7% agarose gel containing ethidium bromide and exposed to UV light for the visualization of amplified products.

- Hybridisation analysis of PCR products: MSRV-pol detection by ELOSA

The protocol was essentially as previously described (21) but with the following modifications: Nunc Maxisorb microtitre plates were coated with 100 ng per well capture probe CpV1b (see Figure 44) either by passive

adsorption (21) or alternatively by using streptavidin coated plates and biotinylated CpV1b. Peroxidase-labelled detector probe DpV1 (see Figure 44) was used and the assay cut-off was defined as the mean of 4 negative controls plus 0.2 OD_{492} units.

- RNA extraction, cDNA synthesis and PCR amplification from MS plasma samples :

Total RNA was extracted from human MS plasma by a guanidium method as described elsewhere (29). Total RNA extracted from 100 ul of plasma, were treated with RNase-free DNase I (0.1U/μl; Boehringer Manheim, France) and reverse transcribed under the conditions recommended by the manufacturer, using Superscript reverse transcriptase (Gibco-BRL, FRANCE). The resulting cDNAs were amplified by semi-nested PCR through 35 cycles (94°C 1 min, 55°C 1 mn, 72°C 1 min 30 sec) and 72°C 8 min for a final extension. Three different fragments in the RT region were amplified by the following specific primers :

- in the protease (PRT) region, for the 1st and 2nd round of PCR, respectively, sense primer [5' TCC AGC AGC AGG ACT GAG GGT 3' (SEQ ID NO:103)] and antisense primers [5' CTG TCC GTT GGG TTT CCT TAC TCC T 3' (SEQ ID NO:104) / 5' GAC AGC AAA TGG GTA TTC CTT TCC 3' (SEQ ID NO:105)]

- in the fragment A of the RT region (Cf. Fig 46), for the 1st and 2nd round of PCR, respectively, sense primer [5' AGG AGT AAG GAA ACC CAA CGG ACA G 3' (SEQ ID NO:106)] and antisense primers [5' TGT ATA TAA TGG TCT GGC TAT TGG G 3' (SEQ ID NO:107) / 5' TTC GGC AGA AAC CTG TTA TGC CAA GG 3' (SEQ ID NO:108)]

- in the fragment B of the RT region (Cf. Fig. 46), for the 1st and 2nd round of PCR, respectively, sense primers [5' GGC TCT GCT CAC AGG AGA TTA GAT AC 3' (SEQ ID NO:109) / 5' AAA GGC ACC AGG GCC CTC AGT GAG GA 3' (SEQ ID NO:110)] and antisense primer 3'[5' GGT TTA AGA GTT GCA CAA GTG CGC AGT C 3' (SEQ ID NO:101)].

The amplified fragments were analysed on ethidium bromide-stained agarose gels, cloned in TA cloning vector (Invitrogen) and sequenced.

2) RESULTS

- Specific retroviral RNA is found in extracellular virions from MS patient-derived cell cultures and in MS patients' CSF.

Choroid plexus cells (4) (obtained post-mortem) and EBV-immortalized peripheral blood B-lymphocytes (30, 31) from MS patients gave rise to cultures expressing 100-120 nm viral particles associated with RT-activity similar to that of the original LM7 isolate (3). Similar cell-types from non-MS donors produced neither this RT-activity nor virions. All the 'infected' cultures were poorly and/or transiently productive and/or had a limited lifespan. Therefore, in order to analyse the genomic RNA present in the very limited quantity of extracellular virions, we used an RT-PCR approach to amplify, with degenerate primers, a conserved region of the pol gene present in all known retroviruses (12); the techniques based on this approach will be called "Pan-retro" RT-PCR. Extensive DNAse treatment of samples and reagents was essential, because human DNA contains many endogenous retroviral elements amplifiable by this technique.

"Pan-retro" RT-PCR experiments were performed on sucrose-density gradient purified virions from supernatants of different types of cell cultures and their non-infected controls: (i) choroid plexus cells sampled post-mortem from MS brain (PLI-1), (ii) choroid plexus cells from non-MS brain autopsy, infected by co-culture with irradiated LM7 cells (LM7P), and (iii) identical non-infected choroid-plexus cells. "Early" B-cell lines obtained by spontaneous in vitro transformation of two EBV-seropositive individuals, (iv) one MS patient and (v) one non-MS control, were also analysed. Figure 43 illustrates the RT-activity in sucrose-gradient fractions obtained

from the B-cell cultures. The technique described by Shih et al. (12) was modified in a semi-nested RT-PCR protocol (27) using degenerate primers (Fig.2) and extensive DNase treatment. PCR amplifications were performed in London (Dpt of Virology, U.C.L.M.S.) on coded aliquots of the density gradient fractions. Blind and systematic cloning and sequencing of the PCR products were undertaken in an independent laboratory (bioMérieux, Lyon). After complete sequencing of 20 to 30 clones per sucrose gradient fraction, the codes were broken and results analysed in parallel with the RT-activity data.

Table 5 presents the distribution of sequences obtained from sucrose gradient fractions containing the peak of viral RT-activity in MS-derived cultures and also the sequences amplified from the corresponding RT-activity negative fractions of uninfected cultures. The predominant sequence detected in bands of the expected size (~140 bp) amplified in all the RT-activity positive fractions (but not in the RT-activity negative fractions) was different from known retroviruses and was designated MSRV-cpol. MSRV-cpol sequences exhibited partial homology (70-75%) with ERV9, a previously described endogenous retroviral sequence (18). A few ERV9 sequences (>90% homology with ERV9) were also present but clearly represented a minority of clones. In addition to typical pol sequences, numerous PCR artefacts (primer multimers, concatemers or single-primer amplifications) related to the use of degenerate primers and low-temperature annealing, were found in all samples (Table 5).

Figure 44 shows an alignment of a consensus sequence of MSRV-*cpol* with the corresponding VLPQG / YMDD region of diverse retroviruses. Figure 45 displays a phylogenic tree based on the evolutionarily conserved amino acid sequences of both exogenous and endogenous retroviruses in this region. From this tree it can be seen that the pol gene of

MSRV is phylogenically related to the C-type group of oncovirinae.

A small scale study was performed to determine the prevalence of MSRV c-pol sequences in the CSF of patients with MS. Identification of MSRV-*cpol* in PCR products by cloning and sequencing is both laborious and time consuming. We therefore devised an enzyme-linked oligosorbent assay (ELOSA), using a capture probe (CpV1B) and a peroxidase-labelled detector probe (DpV1), for the rapid identification of MSRV-*cpol* sequences in `Pan-retrovirus' PCR products (Figure 44). The specificity of this sandwich hybridisation-based assay for HMSRV-*cpol* was tested with both distantly related (HIV and MoMLV) and closely related (ERV9) *pol* sequences. No significant cross reactivity with such targets was observed despite the ability of the ELOSA to detect as little as 0.01 ng of MSRV-*cpol* DNA.

Cerebrospinal fluid (CSF) samples were available from 10 patients with MS and from 10 patients with other neurological disorders. Total RNA was extracted from CSF pellets, reverse transcribed and amplified as above. ELOSA analysis (Table 6) of the PCR products revealed MSRV-*cpol* sequences in 5 of the 10 MS patient samples but in none of the 10 samples from patients with other neurological diseases ($P<0.05$). The presence of MSRV-cpol did not appear to be correlated with age, sex or type of MS, but was seen in untreated patients only (5/6). No patient with immunosuppressive therapy was found positive (0/4). No correlation between MSRV-*cpol* detection and CSF cell count was observed.

- Cloning and sequencing a larger region of the pol gene

An independent identification of the MSRV genomic sequence was obtained by a non-PCR approach using RNA extracted from concentrated virions derived from 2,5 liters of LM7-infected sub-cultures of choroid plexus cells. A limited number of clones was obtained by direct

cloning of the cDNA, one of which (PSJ17) showed partial homology with ERV9 pol. Specific primers based on the MSRV-*cpol* region and on the PSJ17 clone, amplified a 740 bp fragment linking the two independent sequences in RNA extracted from purified virions. PSJ17 was localised on the 3' side of MSRV-*cpol*. Further sequence extension on the 5' side of MSRV-*cpol* and on the 3' side of PSJ17, was obtained using RT-PCR approaches on RNA from purified LM7-like virions produced in MS choroid plexus cultures (4).

In Figure 46, the nucleotide sequence corresponding to overlapping clones obtained by sequence extension in the pol gene is represented with the aminoacid translation corresponding to the putative open reading frames (ORFs) of the protease and of the reverse-transcriptase. The active site motifs of the protease (PRT) and of the reverse-transcriptase (RT) are underlined. In the C-terminal region of the RT sequence, the dispersed amino acid residues regularly present in retroviral RNase H domains, are also underlined.

- Non-degenerate primers detect MSRV-specific RNA in virions associated with the peak of RT-activity . and in in MS patients' plasma

PCR primers (ST1.1 primer set; positions 603-625/1732-1714, on Fig.4) based on overlapping clones in the pol gene, amplified a 1.15 kb segment of the RT region from several different isolates obtained from different MS patients. Nested primers (ST1.2; positions 869-889/1513-1490, on Fig.46) generated a 700 bp fragment (Figure 47) which was more easily visualised by ethidium bromide staining than the first round product generated by ST1.1. The specificity of PCR products was confirmed by stringent hybridisation with a peroxidase-labeled MSRV-*cpol* probe (Fig.44), using the ELOSA technique (21).

The ST1.1 and 2 primer set was used to detect extracellular MSRV RNA in human plasma, although non-optimal for this application. Figure 47 illustrates the

results of PCR amplification of cDNA derived from 2 MS patient and 2 control plasma samples tested in parallel with cDNA from the sucrose density gradient fractions of an MS choroid plexus isolate. Taq-sequencing of the 700 bp bands confirmed the presence of MSRV sequence. A very faint 700 bp band is also visible in fraction 10 which corresponds to the bottom of the tube where aggregated particles usually sediment. Control RT-PCR for cellular aldolase transcripts on plasma-derived RNA was negative, indicating that the results were not due to cellular RNA released by cell lysis during plasma separation. It should be noted that this PCR technique was not designed for epidemiological studies since its sensitivity is impaired by the length of the cDNA required (1.15 kb).

Non degenerate primers amplifying three fragments of the pol gene (the whole protease region, regions A and B of the reverse transcriptase; Cf. Fig. 46) were also used to confirm the presence of MSRV sequences in DNase-treated RNA from MS plasma. These fragments were amplified from the plasma of a further 4 MS patients with active disease. Sequence analysis confirmed that the PRT and RT regions were homologous (>95% and >90% respectively) to MSRV sequences previously obtained on culture virion. No such sequence were detected in plasma from healthy controls (n=4), tested in parallel with MS plasma.

3) DISCUSSION

- Phylogeny of MSRV

From the results of this study, it can be concluded that the virus previously referred to as "LM7" (3, 5, 26) posseses an RNA genome containing the MSRV *pol* sequences described here.

The conserved RT motif of both MSRV and ERV9 is two amino acids shorter than that of other retroviruses, apart from human foamy viruses which nonetheless have a functional RT. The potential ORF encompassing the entire PRT-RT

region is consistent with the virion-associated RT-activity detected in sucrose density gradients with infected culture supernatants. Moreover, since we have recently succeeded in expressing a recombinant protein from the sequence of MSRV protease cloned from MS plasma, we can confirm the reality of the potential PRT ORF. Similar cloning and expression of other sequences containing potential ORFs for MSRV proteins, is being undertaken to confirm their ability to encode enzymes and structural proteins of MSRV virions.

The phylogenic tree in Figure 45, based on the most conserved amino acid sequence in retroviruses (VLPQG...YXDD), shows that the MSRV pol gene is related to the C-type oncoviruses. Apart from ERV9, the closest known retroviral element is RTLV-H, a human endogenous sequence known to have a subtype with a functional pol gene (32). In the *pol* region, this phylogenic affiliation to C-type oncoviruses apparently contradicts our previous assumptions based on the general morphology of the particles observed by electron microscopy (EM), which were compatible with a B or D-type oncovirus (3, 5, 26). However, preliminary data on env sequences detected in MSRV virions, would suggest a greater phylogenic proximity to D-type. Such difference in phylogenies of the pol and env genes have been described in MPMV and suggest a recombinatorial origin in D-type retroviruses (33). D to C type morphological conversion is also possible since it has been reported that a single amino acid substitution in the gag protein can convert retrovirus morphology to that of a different type (34).

- Is MSRV an exogenous retrovirus sharing extensive homology with a related endogenous retrovirus family or an endogenous retrovirus producing extracellular virions?

Southern blot analysis with an MSRV pol probe under stringent conditions, showed hybridisation with a multicopy endogenous family (data not presented),

indicating the existence of endogenous elements more closely related to MSRV than ERV9 itself. Consequently, we were unable to look for a virion-specific provirus in MSRV-producing cells. In agreement with southern blot findings, PCR studies on genomic DNA showed multiple band amplification of MSRV-related endogenous sequences. Since pol is the most conserved retroviral gene, the sequence described here is the least suitable region to discriminate between exogenous and endogenous sequences. It is hoped that sequence information from other parts of the genome may permit such a discrimination, would it be on a tiny portion as has recently been demonstrated for the Jaagsiekte retrovirus (JSRV) of sheep (35). With such sequence data, it would then become possible to identify the MSRV-specific provirus in the genome of virion-producing cell cultures.

MSRV could represent a virion-producing exogenous member of an ERV9-like endogenous family, just as exogenous strains exist in the well-studied mouse mammary tumour virus (MMTV) and murine leukaemia virus (MuLV) retroviral families of mice, and also, in the JSRV retroviral family of sheep (36). Alternatively, it is also conceivable that the extracellular MSRV virions may be produced by a replication-competent endogenous provirus. Wether MSRV is exogenous or endogenous, conceptual similarities exist with the category of retroviruses represented by MuLV, MMTV and JSRV. Unlike defective endogenous elements, this category of agents are known to produce infectious and pathogenic virions, to cause neurological disease (37), solid tumours / leukaemias (36, 38) and to express "endogenous superantigens" (39, 40). Furthermore, in MuLV infections, the genetic endogenous retroviral background of the mouse strain can determine susceptibility or resistance to disease (39, 41). Indeed, such interactions between an infectious retrovirus and its endogenous counterpart may be relevant in the pathogenesis of MS,

since endogenous retroviral genotypes are not identical in all individuals. A genetic control due to related endogenous retroviral genotypes could therefore contribute to the known hereditary susceptibility to MS (43), if MSRV does indeed play an active role in this disease.

Elsewhere, the data in Table 5 suggest that ERV9 elements may be co-expressed, possibly via trans-activation in infected cells, and give rise to heterologous RNA packaging in MSRV virions. Such heterologous packaging is known to occur in other retroviral systems (42).

- A role for the numerous common viruses previously evoked in MS ?

Among the numerous reports of viruses putatively involved in the aetiopathogenesis of MS, a significant proportion focus on two viral families, the paramyxoviridae and the herpesviridae. Regarding the paramyxoviridae, the key observation is of a frequently increased antibody titer to measles virus in MS patients essentially directed, in CSF, against measles fusion protein (44). The existence of aminoacid similarities between conserved domains of the fusion proteins of paramyxoviridae and the transmembrane protein of retroviruses (45), may explain this observation if antigenic cross-reactivity between these two proteins occured.

With regard to the herpesvirus family, the involvement of Epstein-Barr Virus (EBV), Herpes Simplex Virus type 1 (HSV-1) and, most recently, Human Herpes Virus 6 (HHV-6) has been proposed (31, 46, 47). From our previous studies and from those of other groups, it appears that herpesviruses may play an important role in MSRV expression: we have shown that HSV-1 immediate-early ICP0 and ICP4 proteins can transactivate MSRV/LM7 in vitro (6) and Haahr et al. have proposed an important epidemiological role for EBV, as a co-factor in MS, triggering retrovirus reactivation (31). The recent

description by Challoner et al. (47) showing significant expression of HHV6 proteins in MS plaques may also suggest a similar role for HHV6 in the brain.

EXAMPLE 19 : MSRV GENOME DETECTION TECHNIQUE

Following 0.4 μm filtration to remove cellular debris and RNase digestion to remove residual non-encapsidated RNA, serum was processed to extract viral RNA by means of adsorption to a silica matrix. Viral RNA was subjected to DNase digestion, then a combined reverse transcription-PCR (RT-PCR) reaction was performed using primers PTpol-A (sense: 5'xxxx3', SEQ ID NO:183) and PTpol-F (antisense: 5'xxxx3', SEQ ID NO:184). A second round of amplification with nested primers PTpol-B (sense: 5'xxxx3', SEQ ID NO:185) and PTpol-E (antisense: 5'xxxx3', SEQ ID NO:186) generated a 435 bp PCR product which was identified by gel electrophoresis. The specificity of each product was confirmed by dideoxy sequencing. Control reactions without reverse transcriptase were performed to ensure that the products were derived from viral RNA. In addition, to exclude the possibility that the extracted viral RNA might be contaminated with host cell derived nucleic acids, aliquots were tested by nested PCR for the presence of pyruvate dehydrogenase (PDH) DNA and RNA. Samples which generated a signal in either the PDH or the "no-RT" PCR assays were excluded from the analysis.

Sera from patients with clinically active MS and controls were amplified by RT-PCR and sequenced. Virion associated MSRV-RNA was detected in the serum of 10 of 19 (53%) patients with MS but in only 3 of 44 controls without MS (P=0.0001). The control group consisted of 8 patients (all MSRV-RNA negative) with rheumatological disorders and 36 healthy adults. MSRV-RNA titres in both MS patients and controls were apparently low because even moderate dilution of sera (<10 fold) caused loss of signal.

In MS patients, detection of MSRV-RNA was not associated with age, sex, disease duration, or MS type, however a significant negative correlation with treatment was observed. 26 serum samples were obtained from the 19 patients ; 100% of the sera from untreated patients contained detectable MSRV-RNA whereas it was detectable in only 4 of 19 samples (21%) obtained during treatment with corticosteroids and/or azathioprine (P=0.001).

The reason for the apparent loss of virion associated MSRV-RNA during immunosupressive treatment is unknown but the finding is in agreement with the previous observations on the detection of MSRV in cerebrospinal fluid.

TABLE 7

DETECTION OF VIRION ASSOCIATED MSRV-RNA IN MS UNTREATED PATIENTS & CONTROLS

	Positive	Negative	Total	% Positive
Controls without MS[a]	3[b]	41	44	7%
MS sera untreated at time of sampling	7	0	7	100%

[a] The control group consisted of 8 patients with miscellaneous non-MS disorders and 36 healthy adults.

[b] The detection of MSRV RNA in plasma of a few controls in conditions which select virion-packaged RNA, is consistent with the knowledge that a virus associated with MS should be present in a minor proportion of apparently healthy population. Indeed, such individuals can be either healthy carriers or be in the pre-clinical (or sub-clinical) phase of the disease which can last for years.

METHOD :

- Modified SNAP RNA extraction with filtration and RNase digestion

(All centrifugations are at room temperature)

Up to 500 microlitres of serum is filtered using 0.45 micron spin filters (Nanosep MF from Flowgen Catalogue No. U3-0126 Ref. ODM45). The serum is spun for 5 min at 130,000 g (or for further 10 min if necessary).

150 microlitres of filtered serum is incubated with 10 units RNase One (Promega Catalogue No.M4261) for 30 min at 37°C.

The 150 microlitres was then extracted using the SNAP RNA extraction kit (Invitrogen) as below:

- 10 micrograms of poly A RNA was added to the 450 microlitres of Binding Buffer to act as a carrier ; this was then added to the serum and mixed by inversion 6 times ; 300 microlitres of propan-2-ol was then added and mixed by inversion 10 times ; 500 microlitres was transferred to the SNAP column and spun at 1300 g for 1 min and the flow-through discarded ; the remainder was then added to the SNAP column and spun at 1300 g for 1 min and the flow-through discarded ; the column was then washed with 600 microlitres of Super wash and the flow-through discarded ; the column was then washed with 600 microlitres of 1x RNA wash and the flow-through discarded ; this wash was repeated with a 2 min 1300 g spin and the flow-through discarded ; the bound nucleic acid was then eluted by incubating with 135 microlitres of RNase free water for 5 min and spun at 1300 g for 1 min.

- 15 microlitres of 10x DNAse buffer and 3 microlitres (30 units) of DNase I, RNase free (Boehringer Mannheim Cat. No. 776 785) was added and incubated for 30 min at 37°C ; 450 microlitres of Binding Buffer was added and mixed by inversion 6 times ; 300 microlitres of propan-2-ol was then added and mixed by inversion 10 times ; 500 microlitres was transferred to the SNAP column

and spun at 1300 g for 1 min and the flow-through discarded ; the remainder was then added to the SNAP column and spun at 1300 g for 1 min and the flow-through discarded ; the column was then washed with 600 microlitres 1x RNA wash and the flow-through discarded ; this wash was repeated with a 2 min 1300 g spin and the flow-through discarded ; the bound nucleic acid was then eluted by incubating with 105 microlitres of RNase free water for 5 min and spun at 1300 g for 1 min.

- Titan RT-PCR

RT-PCR was performed using the Titan one tube RT-PCR system (Boehringer Mannheim Cat. No. 1 855 476) 25 microlitres of RNA was used in the combined RT-PCR reaction. The total reaction volume was 50 microlitres. Promega rRNAsin (10 units) was the RNase inhibitor used. 170 ng of primers SEQ ID NO:183 and SEQ ID NO:184, respectively, were used. A single master mix was prepared and the sample RNA added last. This was performed at room temperature, not on ice.

The RT step consisted of two sequential 30 min incubations at 50°C and then 60°C. This was immediately followed by the PCR which had the following steps.

* Initial denaturation of template at 94°C for 2 min,
* 40 cycles of 94°C for 30 seconds ; 60°C for 30 seconds ; 68°C for 45 seconds,
* 1 cycle of 68°C for 7 min.

The second round PCR was performed using the Expand long template PCR system (Boehringer Mannheim Cat. No. 1681 842). 0.5 microlitres of the RT-PCR mix was added to 25 microlitres of the round 2 PCR mix. Buffer No. 3 and 50 ng of primers B and E were used. The PCR had the following steps:

* 5 cycles of 94°C for 30 seconds, 60°C for 30 seconds., 68°C for 45 seconds,
* 1 cycle of 68°C for 7 min.

The PCR products were then run on a 2% agarose gel.

The no RT controls were performed using "Expand" PCR system for both rounds. The first round was 40 cycles and the second round 20 cycles.

As a positive control a DNA dilution series was used in both the RT-PCR and the "no RT" PCR. For a result to be valid the RT-PCR and "no-RT" PCRs had to have detected DNA equivalent to between 1 and 0.1 cells.

The analysis of PCR products of an approximately 435 bp fragment in the pol region is shown in Table 8.

TABLE 8

ANALYSIS OF PCR PRODUCTS WITH ORF *

Exp	Disease	Clone	ORF	Fragment (bp)	AA-RT Motif Site
46-7	MS	1	+	429	YGDD
		5	+	429	YGDD
		8	+	429	YGDD
68-1	MS	41	+	438	YMDD
		42	+	438	YMDD
		43	+	438	YMDD

* Defective RNA can also be present in circulating virions, since the fidelity of the MSRV reverse transcriptase appears to be low and since recombination events with related endogenous elements can occur. It is then obvious that the intra- and inter- patients variability can be greater than that illustrated in this example, because of these encapsidated defective MSRV RNA copies.

Table 9 which data have been determined from the alignments of Figures 49 to 53, shows a variability :

- between the clones obtained from the same patient plasma sample in the same PCR amplification experiment ; this means that the patient possesses a virion population which comprises different MSRV variants at a given time,
- between the sequenced variant populations from different patients ; this means that the variants differ from a patient to another patient.

TABLE 9

Degree of identity (percentage) between nucleotide sequences and between peptide sequences, by direct comparison of said sequences (see Figures 49-53)

Patient	68-1	46-7
Nucleotide sequences	between SEQ ID NO:169 and MSRV-pol (SEQ ID NO:1) 90,4 % [b] 92,3 % [a] SEQ ID NOs:170, 171, 172 between them 98,6 % [b] 98,7 % [a]	between SEQ ID NO:176 and MSRV-pol (SEQ ID NO:1) 82,5 % [a] 84 % [b] SEQ ID NOs:177, 178, 179 between them 94,5 % [a] 95,1 % [b]
Peptide sequences	between SEQ ID NOs:173, 174, 175 and SEQ ID NO: 81 % SEQ ID NOs:173, 174, 175 between them 97 %	between SEQ ID NOs:180, 181, 182 and SEQ ID NO: 73,5 % SEQ ID NOs:180, 181, 182 between them 89 %

a) this percentage is determined on the basis of sequences excluding the primers
b) this percentage is determined on the basis of sequences including the primers.

From Figures 53A and 53B, the variability between tested patients sequences can be determined :

- between SEQ ID NO:169 and SEQ ID NO:176 : 16,5 %[a] and 14,8 %[b]
- between the peptide sequences obtained from SEQ ID NO:169 and SEQ ID NO:176 : 20 %.

Four microorganisms are mentioned in the specification page 3 lines 15-26 and they are identified below. They have all been deposited with the ECACC*, in accordance with the provisions of the Budapest Treaty.

- LM7PC deposited on 22nd July 1992 under No. 92072201,
- PLI-2 deposited on 8th January 1993 under No. 93010817,
- POL-2 deposited on 22nd July 1992 under No. V92072202, and
- MS7PG deposited on 8th January 1993 under No. V93010816.

* ECACC : European Collection of Animal Cell Cultures
Vaccine Research and Production Laboratory
Public Health Laboratory Service
Centre of Applied Microbiology and Research
Porton Down
Salisbury, Wiltshire SP4 OJG
United Kingdom

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from patients with multiple sclerosis. Proc. Nat. Acad. Sci. USA 94:7583-7588 (1997).

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: BIO MERIEUX

(ii) TITLE OF THE INVENTION: VIRAL MATERIAL AND NUCLEOTIDE FRAGMENTS ASSOCIATED WITH MULTIPLE SCLEROSIS, FOR DIAGNOSTIC, PROPHYLACTIC AND THERAPEUTIC PURPOSES

(iii) NUMBER OF SEQUENCES: 160

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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
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(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
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(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Dominique GUERRE
(B) REGISTRATION NUMBER:
(C) REFERENCE/DOCKET NUMBER: MD/B05B2679

(ix) TELECOMMUNICATION INFORMATION:
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(B) TELEFAX: 4 72 69 84 31

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1158 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

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CCCTTTGCCA CTACATCAAT TTTAGGAGTA AGGAAACCCA ACGGACAGTG GAGGTTAGTG   60
CAAGAACTCA GGATTATCAA TGAGGCTGTT GTTCCTCTAT ACCCAGCTGT ACCTAACCCT  120
TATACAGTGC TTTCCCAAAT ACCAGAGGAA GCAGAGTGGT TTACAGTCCT GGACCTTAAG  180
GATGCCTTTT TCTGCATCCC TGTACGTCCT GACTCTCAAT TCTTGTTTGC CTTTGAAGAT  240
CCTTTGAACC CAACGTCTCA ACTCACCTGG ACTGTTTTAC CCCAAGGGTT CAGGGATAGC  300
CCCCATCTAT TTGGCCAGGC ATTAGCCCAA GACTTGAGTC AATTCTCATA CCTGGACACT  360
CTTGTCCTTC AGTACATGGA TGATTTACTT TTAGTCGCCC GTTCAGAAAC CTTGTGCCAT  420
CAAGCCACCC AAGAACTCTT AACTTTCCTC ACTACCTGTG GCTACAAGGT TTCCAAACCA  480
AAGGCTCGGC TCTGCTCACA GGAGATTAGA TACTNAGGGC TAAAATTATC CAAAGGCACC  540
AGGGCCCTCA GTGAGGAACG TATCCAGCCT ATACTGGCTT ATCCTCATCC CAAAACCCTA  600
AAGCAACTAA GAGGGTTCCT TGGCATAACA GGTTTCTGCC GAAAACAGAT TCCCAGGTAC  660
ASCCCAATAG CCAGACCATT ATATACACTA ATTANGGAAA CTCAGAAAGC CAATACCTAT  720
TTAGTAAGAT GGACACCTAC AGAAGTGGCT TTCCAGGCCC TAAAGAAGGC CCTAACCCAA  780
GCCCCAGTGT TCAGCTTGCC AACAGGGCAA GATTTTTCTT TATATGCCAC AGAAAAAACA  840
GGAATAGCTC TAGGAGTCCT TACGCAGGTC TCAGGGATGA GCTTGCAACC CGTGGTATAC  900
CTGAGTAAGG AAATTGATGT AGTGGCAAAG GGTTGGCCTC ATNGTTTATG GGTAATGGNG  960
GCAGTAGCAG TCTNAGTATC TGAAGCAGTT AAAATAATAC AGGGAAGAGA TCTTNCTGTG 1020
TGGACATCTC ATGATGTGAA CGGCATACTC ACTGCTAAAG GAGACTTGTG GTTGTCAGAC 1080
AACCATTTAC TTAANTATCA GGCTCTATTA CTTGAAGAGC CAGTGCTGNG ACTGCGCACT 1140
TGTGCAACTC TTAAACCC                                               1158
```

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 297 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

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CCCTTTGCCA CTACATCAAT TTTAGGAGTA AGGAAACCCA ACGGACAGTG GAGGTTAGTG    60
CAAGAACTCA GGATTATCAA TGAGGCTGTT GTTCCTCTAT ACCCAGCTGT ACCTAACCCT   120
TATACAGTGC TTTCCCAAAT ACCAGAGGAA GCAGAGTGGT TTACAGTCCT GGACCTTAAG   180
GATGCCTTTT TCTGCATCCC TGTACGTCCT GACTCTCAAT TCTTGTTTGC CTTTGAAGAT   240
CCTTTGAACC CAACGTCTCA ACTCACCTGG ACTGTTTTAC CCCAAGGGTT CAAGGGA      297
```

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 85 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

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GTTTAGGGAT ANCCCTCATC TCTTTGGTCA GGTACTGGCC CAAGATCTAG GCCACTTCTC    60
AGGTCCAGSN ACTCTGTYCC TTCAG                                          85
```

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 86 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

```
GTTCAGGGAT AGCCCCCATC TATTTGGCCA GGCACTAGCT CAATACTTGA GCCAGTTCTC    60
ATACCTGGAC AYTCTYGTCC TTCGGT                                         86
```

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 85 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

```
GTTCARRGAT AGCCCCCATC TATTTGGCCW RGYATTAGCC CAAGACTTGA GYCAATTCTC    60
ATACCTGGAC ACTCTTGTCC TTYRG                                          85
```

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 85 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

GTTCAGGGAT AGCTCCCATC TATTTGGCCT GGCATTAACC CGAGACTTAA GCCAGTTCTY 60
ATACGTGGAC ACTCTTGTCC TTTGG 85

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 111 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

GTGTTGCCAC AGGGGTTTAR RGATANCYCY CATCTMTTTG GYCWRGYAYT RRCYCRAKAY 60
YTRRGYCAVT TCTYAKRYSY RGSNAYTCTB KYCCTTYRGT ACATGGATGA C 111

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 645 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

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TCAGGGATAG CCCCCATCTA TTTGGCCAGG CATTAGCCCA AGACTTGAGT CAATTCTCAT   60
ACCTGGACAC TCTTGTCCTT CAGTACATGG ATGATTTACT TTTAGTCGCC CGTTCAGAAA  120
CCTTGTGCCA TCAAGCCACC CAAGAACTCT TAACTTTCCT CACTACCTGT GGCTACAAGG  180
TTTCCAAACC AAAGGCTCGG CTCTGCTCAC AGGAGATTAG ATACTNAGGG CTAAAATTAT  240
CCAAAGGCAC CAGGGCCCTC AGTGAGGAAC GTATCCAGCC TATACTGGCT TATCCTCATC  300
CCAAAACCCT AAAGCAACTA AGAGGGTTCC TTGGCATAAC AGGTTTCTGC CGAAAACAGA  360
TTCCCAGGTA CASCCCAATA GCCAGACCAT TATATACACT AATTANGGAA ACTCAGAAAG  420
CCAATACCTA TTTAGTAAGA TGGACACCTA CAGAAGTGGC TTTCCAGGCC CTAAAGAAGG  480
CCCTAACCCA AGCCCCAGTG TTCAGCTTGC CAACAGGGCA AGATTTTTCT TTATATGCCA  540
CAGAAAAAAC AGGAATAGCT CTAGGAGTCC TTACGCAGGT CTCAGGGATG AGCTTGCAAC  600
CCGTGGTATA CCTGAGTAAG GAAATTGATG TAGTGGCAAA GGGTT                   645
```

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 741 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

```
CAAGCCACCC AAGAACTCTT AAATTTCCTC ACTACCTGTG GCTACAAGGT TTCCAAACCA   60
AAGGCTCAGC TCTGCTCACA GGAGATTAGA TACTTAGGGT TAAAATTATC CAAAGGCACC  120
AGGGGCCTCA GTGAGGAACG TATCCAGCCT ATACTGGGTT ATCCTCATCC CAAAACCCTA  180
AAGCAACTAA GAGGGTTCCT TAGCATGATC AGGTTTCTGC CGAAAACAAG ATTCCCAGGT  240
ACAACCAAAA TAGCCAGACC ATTATATACA CTAATTAAGG AAACTCAGAA AGCCAATACC  300
TATTTAGTAA GATGGACACC TAAACAGAAG GCTTTCCAGG CCCTAAAGAA GGCCCTAACC  360
```

CAAGCCCCAG TGTTCAGCTT GCCAACAGGG CAAGATTTTT CTTTATATGG CACAGAAAAA 420
ACAGGAATCG CTCTAGGAGT CCTTACACAG GTCCGAGGGA TGAGCTTGCA ACCCGTGGCA 480
TACCTGAATA AGGAAATTGA TGTAGTGGCA AAGGGTTGGC CTCATNGTTT ATGGGTAATG 540
GNGGCAGTAG CAGTCTNAGT ATCTGAAGCA GTTAAAATAA TACAGGGAAG AGATCTTNCT 600
GTGTGGACAT CTCATGATGT GAACGGCATA CTCACTGCTA AAGGAGACTT GTGGTTGTCA 660
GACAACCATT TACTTAANTA TCAGGCTCTA TTACTTGAAG AGCCAGTGCT GNGACTGCGC 720
ACTTGTGCAA CTCTTAAACC C 741

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 93 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

TGGAAAGTGT TGCCACAGGG CGCTGAAGCC TATCGCGTGC AGTTGCCGGA TGCCGCCTAT 60
AGCCTCTACA TGGATGACAT CCTGCTGGCC TCC 93

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 96 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

TTGGATCCAG TGYTGCCACA GGGCGCTGAA GCCTATCGCG TGCAGTTGCC GGATGCCGCC 60
TATAGCCTCT ACGTGGATGA CCTSCTGAAG CTTGAG 96

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 748 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

TGCAAGCTTC ACCGCTTGCT GGATGTAGGC CTCAGTACCG GNGTGCCCCG CGCGCTGTAG 60
TTCGATGTAG AAAGCGCCCG GAAACACGCG GGACCAATGC GTCGCCAGCT TGCGCGCCAG 120
CGCCTCGTTG CCATTGGCCA GCGCCACGCC GATATCACCC GCCATGGCGC CGGAGAGCGC 180
CAGCAGACCG GCGGCCAGCG GCGCATTCTC AACGCCGGGC TCGTCGAACC ATTCGGGGGC 240
GATTTCCGCA CGACCGCGAT GCTGGTTGGA GAGCCAGGCC CTGGCCAGCA ACTGGCACAG 300
GTTCAGGTAA CCCTGCTTGT CCCGCACCAA CAGCAGCAGG CGGGTCGGCT TGTCGCGCTC 360
GTCGTGATTG GTGATCCACA CGTCAGCCCC GACGATGGGC TTCACGCCCT TGCCACGCGC 420
TTCCTTGTAG ANGCGCACCA GCCCGAAGGC ATTGGCGAGA TCGGTCAGCG CCAAGGCGCC 480
CATGCCATCT TTGGCGGCAG CCTTGACGGC ATCGTCGAGA CGGACATTGC CATCGACGAC 540
GGAATATTCG GAGTGGAGAC GGAGGTGGAC GAAGCGCGGC GAATTCATCC GCGTATTGTA 600
ACGGGTGACA CCTTCCGCAA AGCATTCCGG ACGTGCCCGA TTGACCCGGA GCAACCCCGC 660
ACGGCTGCGC GGGCAGTTAT AATTTCGGCT TACGAATCAA CGGGTTACCC CAGGGCGCTG 720
AAGCCTATCG CGTGCAGTTG CCGGATGC 748

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

GCATCCGGCA ACTGCACG 18

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

GTAGTTCGAT GTAGAAAGCG 20

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

GCATCCGGCA ACTGCACG 18

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

AGGAGTAAGG AAACCCAACG GAC 23

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

TAAGAGTTGC ACAAGTGCG 19

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

TCAGGGATAG CCCCCATCTA T 21

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

AACCCTTTGC CACTACATCA ATTT 24

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURES:

(B) LOCATION: 5, 7, 10, 13

(D) OTHER INFORMATION: G represents inosine (i)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

GGTCGTGCCG CAGGG 15

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

TTAGGGATAG CCCTCATCTC T 21

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

TCAGGGATAG CCCCCATCTA T 21

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 24 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

AACCCTTTGC CACTACATCA ATTT 24

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

GCGTAAGGAC TCCTAGAGCT ATT 23

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

TCATCCATGT ACCGAAGG 18

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

ATGGGGTTCC CAAGTTCCCT 20

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

GCCGATATCA CCCGCCATGG 20

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

GCATCCGGCA ACTGCACG 18

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

CGCGATGCTG GTTGGAGAGC 20

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

TCTCCACTCC GAATATTCCG 20

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 26 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

GATCTAGGCC ACTTCTCAGG TCCAGS 26

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 23 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURES:

(B) LOCATION: 6, 12, 19

(D) OTHER INFORMATION: G represents inosine (i)

(xi) SEQUENCE DESCRIPTION : SEQ ID NO: 32

CATCTGTTTG GGCAGGCAGT AGC 23

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

CTTGAGCCAG TTCTCATACC TGGA 24

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

AGTGYTRCCM CARGGCGCTG AA 22

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

GMGGCCAGCA GSAKGTCATC CA 22

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

GGATGCCGCC TATAGCCTCT AC 22

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

AAGCCTATCG CGTGCAGTTG CC 22

(2) INFORMATION FOR SEQ ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 40 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

TAAAGATCTA GAATTCGGCT ATAGGCGGCA TCCGGCAAGT 40

(2) INFORMATION FOR SEQ ID NO: 39

(i) SEQUENCE CHARACTERISTICS :
(A) LENGTH : 50 amino acids

(B) TYPE : amino acid

(ii) MOLECULE TYPE : peptide

(xi) SEQUENCE DESCRIPTION : SEQ ID NO: 39

```
Asp Ala Phe Phe Cys Ile Pro Val Arg Pro Asp Ser Gln Phe Leu Phe
  1               5                  10                  15
Ala Phe Glu Asp Pro Leu Asn Pro Thr Ser Gln Leu Thr Trp Thr Val
             20                  25                  30
Leu Pro Gln Gly Phe Arg Asp Ser Pro His Leu Phe Gly Gln Ala Leu
         35                  40                  45
Ala Gln
     50
```

(2) INFORMATION FOR SEQ ID NO: 40

(i) SEQUENCE CHARACTERISTICS :

(A) LENGTH : 150 base pairs

(B) TYPE : nucleic acid

(C) STRANDEDNESS : single

(D) TOPOLOGY : linear

(ii) MOLECULE TYPE : cDNA

(xi) SEQUENCE DESCRIPTION : SEQ ID NO: 40

```
GATGCCTTTT TCTGCATCCC TGTACGTCCT GACTCTCAAT TCTTGTTTGC CTTTGAAGAT    60
CCTTTGAACC CAACGTCTCA ACTCACCTGG ACTGTTTTAC CCCAAGGGTT CAGGGATAGC   120
CCCCATCTAT TTGGCCAGGC ATTAGCCCAA                                    150
```

(2) INFORMATION FOR SEQ ID NO: 41

(i) SEQUENCE CHARACTERISTICS :

(A) LENGTH : 11 amino acids

(B) TYPE : amino acid

(ii) MOLECULE TYPE : peptide

(xi) SEQUENCE DESCRIPTION : SEQ ID NO: 41

Cys Ile Pro Val Arg Pro Asp Ser Gln Phe Leu
1 5 10

(2) INFORMATION FOR SEQ ID NO: 42

(i) SEQUENCE CHARACTERISTICS :

(A) LENGTH : 17 amino acids

(B) TYPE : amino acid

(ii) MOLECULE TYPE : peptide

(xi) SEQUENCE DESCRIPTION : SEQ ID NO: 42

Val Leu Pro Gln Gly Phe Arg Asp Ser Pro His Leu Phe Gly Glu Ala
1 5 10 15
Leu
17

(2) INFORMATION FOR SEQ ID NO: 43

(i) SEQUENCE CHARACTERISTICS :

(A) LENGTH : 8 amino acid

(B) TYPE : amino acid

(ii) MOLECULE TYPE : peptide

(xi) SEQUENCE DESCRIPTION : SEQ ID NO: 43

Leu Phe Ala Phe Glu Asp Pro Leu

1 5 8

(2) INFORMATION FOR SEQ ID NO: 44

(i) SEQUENCE CHARACTERISTICS :

(A) LENGTH : 8 amino acids

(B) TYPE : amino acid

(ii) MOLECULE TYPE : peptide

(xi) SEQUENCE DESCRIPTION : SEQ ID NO: 44

Phe Ala Phe Glu Asp Pro Leu Asn
1 5 8

(2) INFORMATION FOR SEQ ID NO: 45

(i) SEQUENCE CHARACTERISTICS :

(A) LENGTH : 25 base pairs

(B) TYPE : nucleic acid

(C) STRANDEDNESS : single

(D) TOPOLOGY : linear

(ii) MOLECULE TYPE : cDNA

(xi) SEQUENCE DESCRIPTION : SEQ ID NO: 45

GTGCTGATTG GTGTATTTAC AATCC 25

(2) INFORMATION FOR SEQ ID NO: 46

(i) SEQUENCE CHARACTERISTICS :

(A) LENGTH : 1859 base pairs

(B) TYPE : nucleic acid

(C) STRANDEDNESS : single

(D) TOPOLOGY : linear

(ii) MOLECULE TYPE : cDNA

(xi) SEQUENCE DESCRIPTION : SEQ ID NO: 46

```
GTGCTGATTG GTGTATTTAC AATCCTTTAT CTAATCCGAA ATGCCCATGT TGCAATATGG   60
AAAGAAAGGG AGTTCCTAAC CTCTGGGGGA ACCCCCATTA AATACCACAA GTAAATCATG  120
GAGTTATTGC ACACAGTGCA AAAACTCAAG GAGGTGGAAG TCTTACACTG CCAAAGCCAT  180
CAGAAAAGGG AAGAGGGGAG AAGAGCAGCA TAAGTGGCTA CAGAGGCAAG GAAAGACTAG  240
CAGAAAGGAA AGAGAGAAAG AGACAGAAAG TCAGAGAGAG AGAGAGGAAG AGACAGAGCA  300
CAAAGAGGGA GTCAGAGAGA GAGAGAGACA GAGAGTCAGA GAGAAGGAAA GAGAGAGAGG  360
AAGAGACAAA GAATGAATCA AACAGAGAGA CAGAAAGTCA GAGAGAGAGA GAGAGAGGAA  420
GAGACAGAGA AAAAGAGGGA GTCAGAAAAA GAGAGACCAA AGAAGAAGTC CAAAGAGAAA  480
GAAAGAGAGA TGGAAGTAGT AAAGGAAAAA CAGTGTACCC TATTCCTTTA AAAGCCGGGG  540
TAAATTTAAA ACCTATAATT GATAACTGAA GGTCTTCTCT GTAACCCTGT AACACTCCAA  600
TACCACCTTG TTGTCAAGTG TAAACAAGGG CGTAGCCCAA AAGCACTGAG GCCACTAACA  660
ACCCATAGCC TTCCTATCAA AATTCCTTAA CCCAGCAGGT TTCCTAACAG GGGATCTAAA  720
TCTTAATTAA TTACCATACA ATGGTCCAAC CAGACTTAGG AGGAATTCCC TTCAGGACGG  780
GAAGATAGAT GCTTCCTCCC AGGCGATTAA GGGAGAAAGA CACAATGGGT ATTCAGTAAG  840
TGCCAAGGGG AACACTTGTA GAAGCAAAGT TAGGAAAATT GCCAAATAAT TGGTTTGCTC  900
AAGAGTTGTT TGCACTCAGC CAAACCTTGA AGTACTTGCA GAATCAGAAA GGAGCCATCT  960
ATACCAATTC TAAGTTAATA TGGACTGAAG GAGGTTTTAT TAATACCAAA GAGAAATTAA 1020
AATCCCAAAC TTATAAGGTT TTCAACCAAA GTAAAGTTTG CTAAAAGTTA ACAGCGTAAC 1080
ATGTATTATC CTACTACCAC ACACTCTCAA AGGATTTCTC AGACAGTTTG CAAGAAATAA 1140
TGATATCTAT CCTTACTCTA CAATCCCAAA TAGACTCTTT GGCAGCAGTG ACTCTCCAAA 1200
ACCGTCAAGG CCTAGACCTC CTCACTGCTG AGAAAGGAGG ACTCTGCACC TTCTTAAGGG 1260
AAGAGTGTTG TCTTTACACT AACCAGTCAG GGATAGTATG AGATGCTGCC CGGCATTTAC 1320
AGAAAAAGGC TTCTGAAATC AGACAACGCC TTTCAAATTC CTATACCAAC CTCTGGAGTT 1380
GGGCAACATG GTTTCTTCCC TTTCTATGTC CCATGGCTGC CATCTTGCTA TTACTCGCCT 1440
TTGGGCCCTG TATTTTTAAC CTCCTTGTCA AATTTGTTTC TTCTAGGATC GAGGCCATCA 1500
AGCTACAGAT GGTCTTACAA ATGGAACCCC AAATGAGCTC AACTATCAAC TTCTACTGAG 1560
GACCCCTAGA CCAACCCCCT GGCCCTTTCA CTGGCCTAAA GAGTTCCCCT CTGGAGGACA 1620
CTACCACTGC AGGGCCCCAT CTTTGCCCCT ATCCAGAAGG AAGTAGCTAG AGCAGTCATT 1680
```

GCCCAATTCC CAAGAGCAGC TGGGGTGTCC CGTTTAGAGT GGGGATTGAG AGGTGAAGCC 1740
AGCTGGACTT CTGGGTCGGG TGGGGACTTG GAGAACTTTT GTGTCTAGCT AAAGGATTGT 1800
AAATGCAACA ATCAGTGCTC TGTGTCTAGC TAAAGGATTG TAAATACACC AATCAGCAC 1859

(2) INFORMATION FOR SEQ ID NO: 47

(i) SEQUENCE CHARACTERISTICS :

(A) LENGTH : 23 base pairs

(B) TYPE : nucleic acid

(C) STRANDEDNESS : single

(D) TOPOLOGY : linear

(ii) MOLECULE TYPE : cDNA

(xi) SEQUENCE DESCRIPTION : SEQ ID NO: 47

TGATGTGAAC GGCATACTCA CTG 23

(2) INFORMATION FOR SEQ ID NO: 48

(i) SEQUENCE CHARACTERISTICS :

(A) LENGTH : 24 base pairs

(B) TYPE : nucleic acid

(C) STRANDEDNESS : single

(D) TOPOLOGY : linear

(ii) MOLECULE TYPE : cDNA

(xi) SEQUENCE DESCRIPTION : SEQ ID NO: 48

CCCAGAGGTT AGGAACTCCC TTTC 24

(2) INFORMATION FOR SEQ ID NO: 49

(i) SEQUENCE CHARACTERISTICS :

(A) LENGTH : 25 base pairs

(B) TYPE : nucleic acid

(C) STRANDEDNESS : single

(D) TOPOLOGY : linear

(ii) MOLECULE TYPE : cDNA

(xi) SEQUENCE DESCRIPTION : SEQ ID NO: 49

GCTAAAGGAG ACTTGTGGTT GTCAG 25

(2) INFORMATION FOR SEQ ID NO: 50:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

CAACATGGGC ATTTCGGATT AG 22

(2) INFORMATION FOR SEQ ID NO: 51:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 400 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

```
GGCTGCTAAA GGAGACTTGT GGTTGTCAGA CAATCGCCTA CTTAGGTACC AGGCCTTATT   60
ACTTGAGGGA CTGGTGCTTC AGATGCGCAC TTGTGCAGCT CTTAACCCAA ACTTATGCTG  120
CCCAGAAGGA TCTTTTAGAG GTCCCCTTAG CCAACCCTGA CCTCAACCTA TATATATACT  180
GATGGAAGTT CGTTTGTAGA AAAGGGATTA CAAAGGGNAG GATATNCCAT AGGTTAGTGA  240
TAAAGCAGTA CTTGAAAGTA AGCCTCTTCC CCCCAGGGAC CAGCGCCCCC GTTAGCAGAA  300
CTAGTGGCAC TGACCCCGAG CCTTAGAACT TGGAAAGGGA GGAGGATAAA TGTGTATACA  360
GATAGCAAGT ATGCTTATCT AATCCGAAAT GCCCATGTTG                        400
```

(2) INFORMATION FOR SEQ ID NO: 52:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2389 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 52:

```
TCAGGGATAG CCCCCATCTA TTTGGTCAGG CACTGGCCCA AGATCTAGGG ACATGCCACT   60
TTTAAGAGCC ATTTCTCAAG TCCAGGTACT CTGGTCCTTC GGTATGTGGA TGATTTACTT  120
TTGGCTACCA GTTCAGTAGC CTCATGCCAG CAGGCTACTC TAGATCTCTT GAACTTTCTA  180
GCTAATCAAG GGTACAAGGC ATCTAGGTTG AAGGCCCAGC TTTGCCTACA GCAGGTCAAA  240
TATCTAGGCC TAATCTTAGC CAGAGGGACC AGGGCACTCA GCAAGGAACA AATACAGCCT  300
ATACTGGCTT ATCCTCACCC TAAGACATTA AAACAGTTGC GGGGGTTCCT TGGAATCACT  360
GGCTTTTTGG TGACTATGGA TTCCCAGATA CAGCAAGATT GGCAGGCCCC TCTATACTGT  420
AATCAAGGAG ACTCACGAGG GCAAGTACTC ATCTAGTAGA ATGGGAACTA GGGACAGAAA  480
CAGCCTTCAA AACCTTAAAG CAGGCCCTAG TACAATCTCC AGCTTTAAGC CTTCCCACAG  540
```

GACAAAACTT CTCTTTATAC ATCACAGAGA GGGCAGAGAT AGCTCTTGGT GTCCTTATTC 600
AGACTCATGG GACTACCCCA CAACCAGTGG CACACCTAAG TAAGGAAATT GATGTAGTAG 660
CAAAAGGCTG GCCTCACTGT TTATGGGTAG CTGTGGTGGT GGCTGTCTTA GTGTCAGAAG 720
CTATCAAAAT AATACAAGGA AAGGATCTCA CTGTCTGGAC TACTCATGAT GTAATGGCAT 780
ACTAGGTGCC AAAAGAAGTT TATGGGTATC AGACAACCAC CTGCTTAGAT ACCAGGGACT 840
ACTCCTGGAG GATTGGGCTT CAAGTGCGTT TTTTGTGGCC TCAACCCTGC CACTTTTCCT 900
CCAGAGGATG GAGAGCCGCT TGAGCATGCT TGCCAACAGG TTGTAGGCCA GAATTATTCC 960
ACCCGAGATG ATCTCTTAGA GTACCCTTAG CTAATCCTGA CCTTAACCTA TATACCAATG 1020
GAAGTTCATT TGTGGAAAAC GGGATATGAA GGGCAGGTTA TGTCATAGTT AGTGATGTAA 1080
TCATACTTGC AAGTAAGCCT CTTACCCCAG GGGCCAGCAC TCAGTTAGCA GAACTAGTCA 1140
CACTTACCTT AACCTTAGAA CTGGGAAAGG GAAAAAGAAT AAATATGTAT ACAGATAGTA 1200
AGTATGCTTA TCTAATCCTA CATGCCCATG CTGCAATATG GAAGGAAAGG GAGTTCCTAA 1260
CCCCTGGGGG AACCCCCATT AAATACCACA AGGYAAATCA TGGAGTTATT GCACGCAGTG 1320
CAAAAACTCA AGGAGGTGGC AGTCTTACAC TGCCGAAGCY ATCAAAAAGG GGAAGGAGAG 1380
GGGAGAACAG CAGCATAAGT GGTTGGCAGA GGCAGTGAAA GACCAGCAGA GAGAAGGAGA 1440
GAGACAACGT CAACGACAGA AGGAAAGAAG AGGAGGAGAC AGAGAGGAAG AGACAGAGAG 1500
ACAGTTAGTC CAAGAGAGAG ACAGAGAGAG GAAGAGACAG ACAGAAAGTC CAAGAGAGAA 1560
GGAAAGAGAG GAAGAGACCA AGGAGTCCNA GAGAGAGAAA GAGATAGAAG TAGTAAAGAA 1620
AAAACATTGT ACCCTATTCC TTTAAAAGCC GGGGTATATT TAAAACCTAT AATTGATAAT 1680
TGAGTTCTTG CACCCTCCTC CAGGGGATYG CTGGGAGGAA ACCCTCAACC GATATGTGAA 1740
AATTGTGGGT CGTCCCTATG TCTCAATTAC CAGCCAATAC CCCCTTGTTT TTAGTGTGAA 1800
CGAGGGTGTA GAGCGCAGAC AGGGAGACCT CTGACAATCC ATACCCTTCC TATCCAAAAT 1860
CCTTAACCCA GCAGGTTTTC TAAAAGGGGA TCTAAATCTT AATTAATTAC CATACAAAGG 1920
TCAAACCAGA TCTAGGAGGA ACTTCCTTCA GGACAGGATG ATAGATGGTT CCTCCCAGGC 1980
GATTAAAGAA AATAAAAAGA CACATGGGCA GCCAGTAAGT GATAAGGGAA CACTAGTAGA 2040
AGCAGTTAGG AGAAGTTGCC TAATAATTGG TCTACTCCAA ATGTGTGAGT TGTTCGCACT 2100
CAGCCCAAAT CTTAAAGTAC TTACAGAATT AGGGAGGAGC CATTTACACC AATTCTAAGT 2160
TAATATGGAC TGGATGAGGT TTTATTAATA GCGAAGGAGA ATTAAATCCT AAACTNACAA 2220
GGTTTTCAAC TAAAGTAAAT TTTACTAAAA GCTAACAGTG TAACATGCAT TATCCTACTA 2280
CAACACACTC TCANAGGATT CCTCAGACAG TTTACAAGAA ATAACAAAAT CTATCTGGTA 2340
AGGATAGTAA CTACAATCCC AAATACATTC TTTGGCAGCA GTGACTCTC 2389

(2) INFORMATION FOR SEQ ID NO: 53:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2448 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 53:

```
TCAGGGATAG CCCCCATCTA TTTGATCAGG CACTAGCCCA AGATCTAGGC CACTTCTGAA   60
GTCCAGGCAT TCTAGTCCTT CAGTATGTGG ATGATTTACT TTTGGCTACC AGTTTGGAAG  120
CCTCATGCCA GCAGGCTACT TGAGATCTCT TGAACTTTCT AGCTAATCAA GGGTGTATGG  180
CATCTAAATT GAAAGTCCAG CTCTGCCTAC AACAAGTCAA ATATCTAGGC CTAATCTTAG  240
ATAGAAGAAC CAGGGCCCTC AGCAAGGAAT GAATAAAGCC TATGCTGGCT TATCGGCACC  300
CTAAGACATT AAAACAATTG TGGGGGTTCC TTGGAATCAC TGGCTTTTGC CGACTATGGA  360
TCCCTGGATA GAGTGAGATA GCCAGGCCCC CTCTATTACT CTTATCAAGG AGACCCAGAG  420
GGCAAATACT TATCTAGTAT TATGGGNACC AGAGGCAGAA AAAGCCTTCC AAACCTTAAA  480
GGAGACCCTA GTACAAGCTC CAGCTTTAAG CCTTCCCACA GGACAAANCT TCTCTTTATA  540
TGTCACAGAG AGAGCAGGAA TAGCTCCTGG AGTCCTTACT CAGACTTTTG GACGACCCCA  600
CGGCCAGTGG CRTACCTAAG TAAGGAAATT GATGTAGTAG CAAAAGGCTG GCCTCACTGT  660
TTATGGGTAG TTGCGGCTGT GGCAGTCTTA CTGTCAAAGG CTATCAAAAT AATACAAGGA  720
AAGGATTTCA CTATCTGGAC TACTCATGAG GAAAATGGCA TATTAGGTGC CAAAGGAAGT  780
TTTTGGCTAT CAGACAACCA CCTGCTCAGA TTCCAGGCAC TACTGATTGA GAGACCAGTG  840
CTTTAAATAT GTATGTGTGT GTGTGGCCCT CAACCCTGCC ACTGTTCTCC CAGAAGATGG  900
AGAACCAATG AAGCATTACT GTCAACAAAT TAGAGTCCAG AGTTATGCTG CCTGAGAGGA  960
TCTCTTAGAA GTCCCCTTAG CTAATCCTGA CCTTAACCTA TATGCTGATG GAAGTTCACT 1020
TGTGGAGAAT GGGATACGAA AAGCACATTA TGCCATAGTT AGTGAGGTAA CAGTACTTGA 1080
AAGTAAGCCT ATTCCCCCAT GGACCAGAGC CCAGTTAGCA GAACTAGTGG CACTTACCCA 1140
AGCCTTAGAA CTAGGAAAGG GAAAAATAAT AAATGTGTAT ACAGATAGCA AGTATGCTTA 1200
TCTAATCCTA CATGCCCATG CTGCAGTATG GAAAGAAAGG GAGTTCCTAA CCTCTGGGGG 1260
AACCCCCATT AAATACCACA AGGCAAATCA TGGAGTTATT GCATGTAGTG CAAAACCTCA 1320
AGTAGGTGGC AGTTTTACAC TGCCTGAAGC TATGGGGAAG GAGAGAGGAG AACAGCAGCA 1380
TAAGTGGCTA GCAGAGGCAG CGAAAGACTA GCAGAGAGGA GAGGTAGGGG AAAGACAGAA 1440
AGTCAAAGAA AAGAAGTCAA AGACAGACAG AGAAAGAGAC AGAGGGAGCC AGAGAGAAAG 1500
AAAAGAGAGA ACGAAAGAGA CAGAATGTCA AAGAACAGAA GAGAGAGGCA GCGCCAGAAG 1560
AGTTAAGAAA GTGAGAAAGA GAGATGGAAA TAGTAAAGAA AAAACAGTGT ACCCTATTCC 1620
```

```
TTTAAAAGCC AGGGTAAATT TAAAACGTAT AATTTTATAA TTGGAAGGTC TTCTCCATAA 1680
CCCTATAACA TTAAAATACC ACCTTGTTGT CAGTGTAAAC AAGAGCATAG CCCAAAAGCA 1740
CTGAGGCCAC TGACAACCCA TAGCCTTCCT ATCAAAAATC CTTAACTCTG CAGGTTTCCT 1800
AACAGGGGAT CTAAATCTCA ACTAATCACC ATACAATGGT CCGACCAGAC CTAGGAGCGA 1860
CTCCCCTCAG GACAGAAGGA TGGATGGTTC CTCCCAGGCC ATTAAGGGAA AGAGACACAA 1920
TGGGTATTCA GTAAGTGATA AGGGAACTCT TGTAGAAGCA GTTAGGAAGA TTGCCTAATA 1980
TTTGGTCTGC TCAAATGTGC CAGCTGTTTG CACTCAGCTA AACCTTAAAT TACTTACAGA 2040
ATTAGGAAGG AGCCATCTAT ACCAATTCTG AGTTAATATG AGCTGAACAA GTTCTTATTA 2100
ATAGCAAAGA ATCATTGAAA TCTCAAACTT GCAAAGTTTT CAACAAAAGT AAAGTTTGCT 2160
GAAAGTTAGC AGTGTAACAT GTATTATCCT AACTTCTAAT CTTGTGGAAA TCAGACCCTA 2220
TCAGTGCCCC TCAAAGCTGA AGTCCATCAG CATATGGCCA TACAACTAAT ACCCCTATTT 2280
ATAGGGTTAG GAATGGCCAC TGCTACAGGA ATGGGAGTAA CAGGTTTATC TACTTCATTA 2340
TCCTATTACC ACACACTCTT AAAGGATTTC TCAGACAGTT TACAAGAAAT AACAAAATCT 2400
ATCCTTACTC TNTARTCCCA AATAGRTTCT TTGGCAGCAG TGACTCTC             2448
```

(2) INFORMATION FOR SEQ ID NO: 54:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 54:

```
CCTGAGTTCT TGCACTAACC C                21
```

(2) INFORMATION FOR SEQ ID NO: 55:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 55:

GTCCGTTGGG TTTCCTTACT CCT 23

(2) INFORMATION FOR SEQ ID NO: 56:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1196 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 56:

TTCCTGAGTT CTTGCACTAA CCTCAAATGA GAGAAGTGCC GCCATAACTG CAACCCAAGA 60
GTTTGGCGAT CCCTGGTATC TCAGTCAGGT CAATGACAGG ATGACAACAG AGGAAAGATA 120
ATGATTCCCC ACAGGCCAGC AGGCAGTTCC CAGTGTAGAC CCTCATTAGG ACACAGAATC 180
AGAACATGGA GATTGGTGCC GCAGACATTT GCTAACTTGC GTGCTAGAAG GACTAAGGAA 240
AACTAGGAAG ATATGAATTA TTCAATGATG TCCACTATAA CACAGGGGAA AGGAAGAAAA 300
TCCTACTGCC TTTCTGGAGA GACTAAGGGA GGCATTGAGG AAGCATACCA GGCAAGTGGA 360
CATTGGAGGC TCTGGAAAAG GGAAAAGTTG GGAAAAGTAT ATGTCTAATA GGGCTTGCTT 420
CCAGTGTGGT CTACAAGGAC ACTTTAAAAA AGATTGTCCA ATAGAAATAA GCCACCACCT 480
CGTCCATGCC CCTTATGTCA AGGGAATCAC TGGAAGGCCC ACTGCCCCAG GGGATGAAGG 540
TCCTCTGAGT CAGAAGCCAC TAACCAGATG ATCCAGCAGC AGGACTGAGG GTGCCCGGGG 600
CAAGCGCCAG CCCATGCCAT CACCCTCACA GAGCCCCAGG TATGCTTGAC CATTGAGGGT 660
CAGAAGGGTA CTGTCTCCTG GACACTGGCG GGCCTTCTCA GTCTTACTTT CCTGTCCTGG 720
ACAACTGTCC TCCAGATCTG TCACTGTCCG AGGGGTCCTA GGACAGCCAG TCACTAGATA 780
CTTCTCCCAG CCACTAAGTT GTGACTGGGG AACTTTACTC TTCCACATGC TTTTCTAATT 840

```
ATGCCTGAAA GCCCCACTCT CTTGTTAGGG GAGAGACATT CTAGCAAAAG CAGGGGCCAT  900
TATACATGTG AATATAGGAG AAGGAACAAC TGTTTGTTGT CCCCTGCTTG AGGAAGGAAT  960
TAATCCTGAA GTCCGGGCAA CAGAAGGACA ATATGGACAA GCAAAGAATG CCCGTCCTGT 1020
TCAAGTTAAA CTAAAGGATT CCACCTCCTT TCCCTACCAA AGGCAGTACC CCCTCAGACC 1080
CGAGACCCAA CAAGAACTCC AAAAGATTGT AAAGGACCTA AAAGCCCAAG GCCTAGTAAA 1140
ACCAAGCAAT AGCCCTTGCA AGACTCCAAT TTTAGGAGTA AGGAAACCCA ACGGAC     1196
```

(2) INFORMATION FOR SEQ ID NO: 57:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2391 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 57:

```
ATGATCCAGC AGCAGGACNG AGGGTGCCCG GGGCAAGCGC CAGCCCATGC CATCACCCTC   60
ACAGAGCCCC AGGTATGCTT GACCATTGAG GGTCAGAAGG GTNACTGTCT CCTGGACACT  120
GGCGGNGCCT TCTCAGTCTT ACTTTCCTGT CCTGGACAAC TGTCCTCCAG ATCTGTCACT  180
GTCCGAGGGG TCCTAGGACA GCCAGTCACT AGATACTTCT CCCAGCCACT AAGTTGTGAC  240
TGGGGAACTT TACTCTTCCC ACATGCTTTT CTAATTATGC CTGAAAGCCC CACTCTCTTG  300
TTGGGGAGAG ACATTCTAGC AAAAGCAGGG GCCATTATAC ATGTGAATAT AGGAGAAGGA  360
ACAACTGTTT GTTGTCCCCT GCTTGAGGAA GGAATTAATC CTGAAGTCCG GGCAACAGAA  420
GGACAATATG GACAAGCAAA GAATGCCCGT CCTGTTCAAG TTAAACTAAA GGATTCCACC  480
TCCTTTCCCT ACCAAAGGCA GTACCCCCTC AGACCCGAGA CCCAACAAGA ACTCCAAAAG  540
ATTGTAAAGG ACCTAAAAGC CCAAGGCCTA GTAAAACCAA GCAATAGCCC TTGCAAGACT  600
CCAATTTTAG GAGTAAGGAA ACCCAACGGA CAGTGGAGGT TAGTGCAAGA ACTCAGGATT  660
ATCAATGAGG CTGTTGTTCC TCTATACCCA GCTGTACCTA ACCCTTATAC AGTGCTTTCC  720
CAAATACCAG AGGAAGCAGA GTGGTTTACA GTCCTGGACC TTAAGGATGC CTTTTTCTGC  780
ATCCCTGTAC GTCCTGACTC TCAATTCTTG TTTGCCTTTG AAGATCCTTT GAACCCAACG  840
TCTCAACTCA CCTGGACTGT TTTACCCCAA GGGTTCAGGG ATAGCCCCCA TCTATTTGGC  900
CAGGCATTAG CCCAAGACTT GAGTCAATTC TCATACCTGG ACACTCTTGT CCTTCAGTAC  960
```

```
ATGGATGATT TACTTTTAGT CGCCCGTTCA GAAACCTTGT GCCATCAAGC CACCCAAGAA 1020
CTCTTAACTT TCCTCACTAC CTGTGGCTAC AAGGTTTCCA AACCAAAGGC TCGGCTCTGC 1080
TCACAGGAGA TTAGATACTN AGGGCTAAAA TTATCCAAAG GCACCAGGGC CCTCAGTGAG 1140
GAACGTATCC AGCCTATACT GGCTTATCCT CATCCCAAAA CCCTAAAGCA ACTAAGAGGG 1200
TTCCTTGGCA TAACAGGTTT CTGCCGAAAA CAGATTCCCA GGTACASCCC AATAGCCAGA 1260
CCATTATATA CACTAATTAN GGAAACTCAG AAAGCCAATA CCTATTTAGT AAGATGGACA 1320
CCTACAGAAG TGGCTTTCCA GGCCCTAAAG AAGGCCCTAA CCCAAGCCCC AGTGTTCAGC 1380
TTGCCAACAG GGCAAGATTT TTCTTTATAT GCCACAGAAA AAACAGGAAT AGCTCTAGGA 1440
GTCCTTACGC AGGTCTCAGG GATGAGCTTG CAACCCGTGG TATACCTGAG TAAGGAAATT 1500
GATGTAGTGG CAAAGGGTTG GCCTCATNGT TTATGGGTAA TGGNGGCAGT AGCAGTCTNA 1560
GTATCTGAAG CAGTTAAAAT AATACAGGGA AGAGATCTTN CTGTGTGGAC ATCTCATGAT 1620
GTGAACGGCA TACTCACTGC TAAAGGAGAC TTGTGGTTGT CAGACAACCA TTTACTTAAN 1680
TATCAGGCTC TATTACTTGA AGAGCCAGTG CTGNGACTGC GCACTTGTGC AACTCTTAAA 1740
CCCAAACTTA TGCTGCCCAG AAGGATCTTT NTAGAGGTCC CCTTAGCCAA CCCTGACCTC 1800
AACTATATAT ATACTGATGG AAGTTCGTTT GTAGAAAAGG GATTACAAAG GGNAGGATAT 1860
NCCATAGGTG TTAGTGATAA AGCAGTACTT GAAAGTAAGC CTCTTCCCCC CCAGGGACCA 1920
GCGCCCCCGT TAGCAGAACT AGTGGCACTG ACCCCGCGAG CCTTAGAACT TTGGAAAGGG 1980
AGGAGGATAA ATGTGTATAC AGATAGCAAG TATGCTTATC TAATCCGAAA TGCCCATGTT 2040
GTTTATCTAA TCCGAAATGC CCATGTTGCA ATATGGAAAG AAAGGGAGTT CCTAACCTCT 2100
GGGGGAACCC CCATTAAATA CCACAAGTTA ATCATGGAGT TATTGCACAC AGTGCAAAAA 2160
CTCAAGGAGG TGGAAGTCTT ACACTGCCAA AGCCATCAGA AAAGGGAAAG GGGAGAAGAG 2220
CAGCATAAGT GGCTACAGAG GCAAGGAAAG ACTAGCAGAA AGGAAAGAGA GAAAGAGACA 2280
GAAAGTCAGA GAGAGAGAGA GGAAGAGACA GAGCACAAAG AGGGAGTCAG AGAGAGAGAG 2340
AGACAGAGAG TCAGAGAGAA GGAAAGAGAG AGAGGAAGAG ACAAAGAATG A          2391
```

(2) INFORMATION FOR SEQ ID NO: 58:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1722 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 58:

```
TGGAGAATAG CAGCATAAGT TGGCTGGCAG AAGTAGGGAA AGACAGCAAG AAGTAAAGAA   60
AAAAARGAGA AAGTCAGAGA AAGAAAAAAA GAGAGGAAGA AACAAAGAAG AACTTGAAGA  120
GAGAAAGAAG TAGTAAAGAA AAAACAGTAT ACCCTATTCC TTTAAAAGCC AGGGTAAATT  180
TCTGTCTACC TAGCCAAGGC ATATTCTTCT TATGTGGAAC ATCAACCTAT ATCTGCCTCC  240
CCACTAACTG GACAGGCACC TGAACCTTAG TCTTTCTAAG TCCCAACATT AACATTGCCC  300
CAGGAAATCA GACCCTATTG GTACCTGTCA AAGCTAAAGT CCCGTCAGTG CAGAGCCATA  360
CAACTAATAT CCCTATTTAT AGGGTTAGGA ATGGCTACTG CTACAGGAAC TGGAATAGCC  420
GGTTTATCTA CTTCATTATC CTACTACCAT ACACTCTCAA AGAATTTCTC AGACAGTTTG  480
CAAGAAATAA TGAAATCTAT TCTTACTTTA CAATCCCAAT TAGACTCTTT GGCAGCAATG  540
ACTCTCCAAA ACCGCCGAGG CCCACACCTC CTCACTGCTG AGAAAGGAGG ACTCTGCACC  600
TTCTTAGGGG AAGAGTGTTG TTTTTACACT AACCAGTCAG GGATAGTACG AGATGCCACC  660
TGGCATTTAC AGGAAAGGGC TTCTGATATC AGACAATGCC TTTCAAACTC TTATACCAAC  720
CTCTGGAGTT GGGCAACATG GCTTCTTCCA TTTCTAGGTC CCATGGCAGC CATCTTGCTG  780
TTACTCACCT TTGGGCCCTG TATTTTTAAG CTTCTTGTCA AATTTGTTTC CTCTAGGATC  840
GAAGCCATCA AGCTACAGAT GGTCTTACAA ATGGAACCCC AAATGAGTTC AACTAACAAC  900
TTCTACCAAG GACCCCTGGA ACGATCCACT GGCACTTCCA CTAGCCTAGA GATTCCCCTC  960
TGGAAGACAC TACAACTGCA GGGCCCCTTC TTTGCCCCTA TCCAGCAGGA AGTAGCTAGA 1020
GCGGTCATCG GCCAAATTCC CAACAGCAGT TGGGGTGTCC TGTTTAGAGG GGGGATTGAA 1080
GAGGTGACAG CCTGCTGGCA GCCTCACAGC CCTCGTTGGY TCTCAGTGCC TCCTCAGCCT 1140
TGGTGCCCAC TCTGGCCGTG CTTGAGGAGC CCTTCAGCCT GCCACTGCAC TGTGGGAGCC 1200
TCTTTCTGGG CTGGACAAGG CCGGAGCCAG CTCCCTCAGC TTGCAGGGAG GTATGGAGGG 1260
AGAGATGCAG GCGGGAACCA GGGCTGCGCA TGGCGCTTGC GGGCCAGCAT GAGTTCCAGG 1320
TGGGCGTGGG CTCGGCGGGC CCCACACTCG GGCAGTGAGG GGCTTAGCAC CTGGGCCAGA 1380
CAGATGCTGT GCTCAACTTC TTCGCTGGGC CTTAGCTGCC TTCCCCGTGG GGCAGGGCTY 1440
CGGGAACMTG CAGCCTGCCC ATGCTTGAGC CCCCCACCCC GCCGTGGGTT CYTGCACAGC 1500
CCAAGCTTCC CGGACAAGCA CCACCCCTTA TCCACGGTGC CCAGTCCCAT CAACCACCCA 1560
AGGGTTGAGG AGTGCGGGCA CACAGCGCGG GATTGGCAGG CAGTTCCACT TGCGGCCTTG 1620
GTGCGGGATC CACTGCGTGA AGCCAGCTGG GCTCCTGAGT CTGGTGGGGA CTTGGAGAAT 1680
CTTTATGTCT AGCTAAGGGA TTGTAAATAC ACCAATCAGC AC                   1722
```

(2) INFORMATION FOR SEQ ID NO: 59:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 495 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 59:

```
CTTCCCCAAC TAATAAGGAC CCCCCTTTCA ACCCAAACAG TCCAAAAGGA CATAGACAAA   60
GGAGTAAACA ATGAACCAAA GAGTGCCAAT ATTCCCTGGT TATGCACCCT CCAAGCGGTG  120
GGAGAAGAAT TCGGCCCAGC CAGAGTGCAT GTACCTTTTT CTCTCTCACA CTTGAAGCAA  180
ATTAAAATAG ACNTAGGTNA ATTNTCAGAT AGCCCTGATG GYTATATTGA TGTTTTACAA  240
GGATTAGGAC AATCCTTTGA TCTGACATGG AGAGATATAA TATTACTGCT AAATCAGACG  300
CTAACCTCAA ATGAGAGAAG TGCTGCCATA ACTGGAGCCC GAGAGTTTGG CAATCTCTGG  360
TATCTCAGTC AGGTCAATGA TAGGATGACA ACGGAGGAAA GAGAACGATT CCCCACAGGG  420
CAGCAGGCAG TTCCCAGTGT AGCTCCTCAT TGGGACACAG AATCAGAACA TGGAGATTGG  480
TGCCGCAGAC ATTTA                                                   495
```

(2) INFORMATION FOR SEQ ID NO: 60:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2503 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 60:

```
CCAAGAACCC ACCAATTCCG GANCACATTT TGGCGACCAC GAAGGGACTT TCGCATATCG   60
CCAAGCGGTG AGACAATAGC CGAGCGGTGA GACCTTTCCC AATCGCCAAG CAGTGAGTAC  120
CATCAGACCC CTTTCACTTG CTATTCTGTC CTATCTTTCT TTAGAATTCG GGGGCTAAAT  180
ACCGGGCATC TGTCAGCCAT TTAAAAGTGA CTAGCGGGCC GCCGGACTAA AGACACGGGT  240
```

GTCAAGCTTT CTGGGAAAGG GCTCTCTAAC AACCCCCAAC TCTTTGGAGT TGGGACCGTT 300
GGTTTGCCTA GAACCAGCTT CCGCTTTTCC TGTACTTCTG GGCTGAGCCG TGGGTTGACA 360
GTGAAGGAAA GCCATGCATC TCCGGGGTCT CGMCAACATG TTGGTTGACC CTGCGGCCAT 420
GAGTGGAACT CTCAAAAGCA TGTCGCCCAA GCGACACTCG CCTATCTATC CTATCTATCC 480
TGACCCTTGC CCTCTGGGTC CTAATGCCTG CCAGACAAAC TTCCTCTCGC CTCTCTTCTC 540
TGAAGCTAGA ACCGCTTCTA AAAATTGCTA CCTGGTCTCT GGTGCTTTTC CTARTTTCTC 600
CTATAAAGAA TGAWTTCTAG TATTAAACTC CAGGACTCTG TTACCTTCTT TAGGCACCCG 660
GGCTCACCAA TCAGAAAGAC ACAGTTTTTG CCCAAGGCCC CATCGTAGTG GGGACTACCT 720
GGAATTTTAG GATCCCTCCT CAGACTAACA GGCCTAACAA AAGTTATTCC TGAAGCTAGG 780
ATATGGGGAG CCTCAGAAAT TGTATCCCTC CTATTCATAT AAGTGAGAAC AAAAGGTGTC 840
ACTCTTCCAA CCCTGAAGAT CCCCTCCCTC CCTCAGGGTA TGGCCCTCCA TTTCATTTTT 900
GTGGCATAAC ATCTTTATAG GATGGGGTAA AGTCCCAATA CTAACAGGAG AATGCTTAGG 960
ACTCTAACAG GTTTTTGAGA ATGCGTCAGT AAGGGCCACT AAATCTGATT TTTCTCAGTC 1020
GGTCCTCCTT GTGGTCTAGG AGGACAGGCA AGGTTGTGCA GGTTTTCGAG AATGCGTCAG 1080
TAAGGACCAC TAAATCCGAC CTTCCTCGGT CCTCCATGTG GTCTGGGAGG AAAACTAGTG 1140
TTTCTGCTGC TGCGTCGGTG AGCGCAACTA TTCAAGTCAG CAGGGTCCAG GGACCGTTGC 1200
AGGTTCTTGG GCAGGGGTTG TTTCTGCTGC TGCATTGGTG AATGCAACTA TTCTGATCAG 1260
CAGGGTCCCA GGACCATTGC AGGTCCTTGG GCAGGGAGAG AAACAAAACA AACCAAAACT 1320
GTGGGCGGTT TTGTCTTTCA TATGGGAAAC ACTCAGGCAT CAACAGGTTC ACCCTTGAAA 1380
TGCATCCTAA GCCATTGGGA CCAATTTGAC CCACAAACCC TGAAAAAGAG GAGGCTCATT 1440
TTTTCCTGCA CTACGGCTTG GCCCCAATAT TCTCTTTYTG ATGGGGAAAA ATGGCCACCT 1500
GAGGGAAGCA CAAATTACAA TAYTATCCTA CAGCYTGATC TTTTCTGTAA GAGGGAAGGC 1560
AAATGGAGTG AATACCTTAT GTCCAAGCTT TCTTTTCATT GAGGGAGAAT ACACAACTAT 1620
GCAAAGCTTG CAATTTACAT CCCACAGGAG GACCCTTCAG CTTACCCCCA TATCCTAGCC 1680
TCCCTATAGC TTCCCTTCCT ATTGATGATA CTCCTCCTCT AATCTCCCCT GCCCAGAAGG 1740
AAATAAGCAA AGAAATCTCC AAAGGTCCAC AAAAACCCCC GGGCTATCGG TTATGTCCCT 1800
TCAAGYTGTA GGGGGAGGGG AATTTGGCCC AACCCGGGTG CATGTCCCTT CTCCCTCTCT 1860
GATTTAAAGC AGATCAAGGC AGACCTGGGG AAGTTTTCAG ATGATCCTGA TAGGTACATA 1920
GATGTCCTAC AGGGTCTAGG GCAAACCTTT GACCTCACTT GGAGAGACGT CATGCTACTG 1980
TTAGATCAAA CCCTGGCCTT TAATGAAAAG AATGCGGCTT TAGCTGCAGC CTGAGAGTTT 2040
GGAGATACCT GGTATCCTAG TCAAGTAAAT GAAAGAATGA CAGCCGAAGA AAGGGACAAC 2100
TTCCTTACTG GTCAGCAACC CATCCCCAGT ATGGATCCCC ACTGGGACTT TGACTCAGAT 2160
CATGGGGACT GGAGTCGTAA ACATCTGTTG ATCTGTGTTC TGGAAGGACT AAGGAGAATT 2220
GGGAAAAAGC CCATGAATTA TTCAATGATA TCCACCATAA CCCAGGGAAA GGAAGAAAAT 2280
CCTTCTGCCT TCCTCGAGCG GCTACAAGAG GCCTTAAGAA AATATACTCC CCTGTCACCC 2340
GAATCACTCG AGGGTCAATT GATTCTAAAA GATAAGTTTA TTACCCAATC AGCCACAGAT 2400

ATCAGGAGAA AGCTCCAAAA GCAAGCCCTG AGCCTGAACA AAATCTAGAG ACATTATTAA 2460
ACCTGGCAAC CTTGGTGTTC TATAATAGGG ACCAAGAGGA ACA 2503

(2) INFORMATION FOR SEQ ID NO: 61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1167 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 61:

AAGGAAACTC AGAAAGCCAA TACCCATTTA GTAAGATGGA CACCAGAAGC AGAAGCAGCT 60
TTCCAGGCCC TAAAGAAATC CCTAACCCAA GCCCCAGTGT TAAGCTTGCC AACGGGGCAA 120
GACTTTTCTT TATATGTCAC AGAAAAACAG GAATAGCTCT AGGAGTCCTT ACACAGGTCC 180
AAGGGACAAG CTTGCAACCT GTGGCATACC TGAGTAAGGA AACTGATGTA NTGGCAAAGG 240
GTTGGCCTCA TTGTTTACAG GTAGGGCAGC AGTAGCAGTC TTAGTTTCTG AAACAGTTAA 300
AATAATACAG GGAAGAGATC TTACTGTGTG GACATCTCAT GATGTGAACG GCATACTCAC 360
TGCTAAAGAG GACTTGTGGC TGTCAGACAA CCATTTACTT AAATAGCAGG TTCTATTACT 420
TGAAGTGCCA GTGCTGCGAC TGCACATTTG TGCAACTCTT AACCCAGCCA CATTTCTTCC 480
AGACAATGAA GAAAAGATAG AACATAACTG TCAACAAGTA ATTGCTCAAA CCTATGCTGC 540
TCGAGGGGAC CTTCTAGAGG TTCCCTTGAC TGATCCCGAC CTCAACTTGT ATACTGATGG 600
AAGTTCCTTG GCAGAAAAAG GACTTTGAAA AGCGGGGTAT GCAGTGATCA GTGATAATGG 660
AATACTTGAA AGTAATCGCC TCACTCCAGG AACTAGTGCT CACCTGGCAG AACTAATAGC 720
CCTCACTTGG GCACTAGAAT TAGGAGAAGG AAAAAGGGTA AATATATATT CAGACTCTAA 780
GTATGCTTAC CTAGTCCTCC ATGCCCATGC AGCAATATGG AGAGAGAGGG AATTCCTAAC 840
TTCTGAGGGA ACACCTATCA ACCATCAGGG AAGCCATTAG GAGATTATTA TTGGCTGTAC 900
AGAAACCTAA AGAGGTGGCA GTCTTACACT GCCAGGGTCA TCAGGAAGAA GAGGAAAGGG 960
AAATAGAAGG CAATCGCCAA GCGGATATTG AAGCAAAAAA AGCCGCAAGG CAGGACTCTC 1020
CATTAGAAAT GCTTATAGAA GGACCCCTAG TATGGGGTAA TCCCCTCTGG GAAACCAAGC 1080
CCCAGTACTC AGCAGGAAAA ATAGAATAGG AAACCTCACA AGGACATACT TTCCTCCCCT 1140
CCAGATGGCT AGCCACTGAG GAAGGAA 1167

(2) INFORMATION FOR SEQ ID NO: 62:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 78 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 62:

```
TCCAAAGGCA CCAGGGCCCT CAGTGAGGAA CGTATCCAGC CTATACTGGC TTATCCTCAT    60
CCCAAAACCC TAAAGCAA                                                  78
```

(2) INFORMATION FOR SEQ ID NO: 63

(i) SEQUENCE CHARACTERISTICS :

(A) LENGTH : 26 amino acids

(B) TYPE : amino acid

(ii) MOLECULE TYPE : peptide

(xi) SEQUENCE DESCRIPTION : SEQ ID NO: 63

```
Ser Lys Gly Thr Arg Ala Leu Ser Glu Glu Arg Ile Gln Pro Ile Leu
 1               5                  10                  15
Ala Tyr Pro His Pro Lys Thr Leu Lys Gln
            20                  25
```

(2) INFORMATION FOR SEQ ID NO: 64:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 64:

AAATGTCTGC GGCACCAATC TCCATGTT 28

(2) INFORMATION FOR SEQ ID NO: 65:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 65:

AAGGGGCATG GACGAGGTGG TGGCTTATTT 30

(2) INFORMATION FOR SEQ ID NO: 66:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 66:

GGAGAAGAGC AGCATAAGTG G 21

(2) INFORMATION FOR SEQ ID NO: 67:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 67:

GTGCTGATTG GTGTATTTAC AATCC 25

(2) INFORMATION FOR SEQ ID NO: 68:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 34 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 68:

GACTCGCTGC AGATCGATTT TTTTTTTTTT TTTT 34

(2) INFORMATION FOR SEQ ID NO: 69:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 69:

GCCATCAAGC CACCCAAGAA CTCTTAACTT 30

(2) INFORMATION FOR SEQ ID NO: 70:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 70:

CCAATAGCCA GACCATTATA TACACTAATT 30

(2) INFORMATION FOR SEQ ID NO: 71:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 71:

GCCATAACTG CAACCCAAGA GTT 23

(2) INFORMATION FOR SEQ ID NO: 72:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 72:

GGACGAGGTG GTGGCTTATT TCT 23

(2) INFORMATION FOR SEQ ID NO: 73:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 73:

AACTTGCGTG CTAGAAGGAC TAAGG 25

(2) INFORMATION FOR SEQ ID NO: 74:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 74:

AACTTTTCCC TTTTCCAGAT CCTC 24

(2) INFORMATION FOR SEQ ID NO: 75:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 75:

GCATACCAGG CAAGTGGACA TT 22

(2) INFORMATION FOR SEQ ID NO: 76:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 76:

CTGTCCGTTG GGTTTCCTTA CTCCT 25

(2) INFORMATION FOR SEQ ID NO: 77:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 77:

GAGGCTCTGG AAAAGGGAAA AGTT 24

(2) INFORMATION FOR SEQ ID NO: 78:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 78:

CTGTCCGTTG GGTTTCCTTA CTCCT 25

(2) INFORMATION FOR SEQ ID NO: 79:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 79:

AGGAGTAAGG AAACCCAACG GACAG 25

(2) INFORMATION FOR SEQ ID NO: 80:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 80:

TGTATATAAT GGTCTGGCTA TTGGG 25

(2) INFORMATION FOR SEQ ID NO: 81:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 81:

AGGAGTAAGG AAACCCAACG GACAG 25

(2) INFORMATION FOR SEQ ID NO: 82:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 82:

TTCGGCAGAA ACCTGTTATG CCAAGG 26

(2) INFORMATION FOR SEQ ID NO: 83:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 83:

CTCGATTTCT TGCTGGGCCT TA 22

(2) INFORMATION FOR SEQ ID NO: 84:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 84:

GTTGATTCCC TCCTCAAGCA 20

(2) INFORMATION FOR SEQ ID NO: 85:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 85:

CTCTACCAAT CAGCATGTGG 20

(2) INFORMATION FOR SEQ ID NO: 86:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 86:

```
TGTTCCTCTT GGTCCCTAT                    19
```

(2) INFORMATION FOR SEQ ID NO: 87:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 433 aminoacids

(B) TYPE: aminoacid

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 87:

```
Met Ala Thr Ala Thr Gly Thr Gly Ile Ala Gly Leu Ser Thr Ser Leu
1               5                   10                  15
Ser Tyr Tyr His Thr Leu Ser Lys Asn Phe Ser Asp Ser Leu Gln Glu
            20                  25                  30
Ile Met Lys Ser Ile Leu Thr Leu Gln Ser Gln Leu Asp Ser Leu Ala
        35                  40                  45
Ala Met Thr Leu Gln Asn Arg Arg Gly Pro His Leu Leu Thr Ala Glu
    50                  55                  60
Lys Gly Gly Leu Cys Thr Phe Leu Gly Glu Glu Cys Cys Phe Tyr Thr
65                  70                  75                  80
Asn Gln Ser Gly Ile Val Arg Asp Ala Thr Trp His Leu Gln Glu Arg
                85                  90                  95
Ala Ser Asp Ile Arg Gln Cys Leu Ser Asn Ser Tyr Thr Asn Leu Trp
            100                 105                 110
```

```
Ser Trp Ala Thr Trp Leu Leu Pro Phe Leu Gly Pro Met Ala Ala Ile
        115                 120                 125
Leu Leu Leu Leu Thr Phe Gly Pro Cys Ile Phe Lys Leu Leu Val Lys
    130                 135                 140
Phe Val Ser Ser Arg Ile Glu Ala Ile Lys Leu Gln Met Val Leu Gln
145                 150                 155                 160
Met Glu Pro Gln Met Ser Ser Thr Asn Asn Phe Tyr Gln Gly Pro Leu
                165                 170                 175
Glu Arg Ser Thr Gly Thr Ser Thr Ser Leu Glu Ile Pro Leu Trp Lys
            180                 185                 190
Thr Leu Gln Leu Gln Gly Pro Phe Phe Ala Pro Ile Gln Gln Glu Val
        195                 200                 205
Ala Arg Ala Val Ile Gly Gln Ile Pro Asn Ser Ser Trp Gly Val Leu
    210                 215                 220
Phe Arg Gly Gly Ile Glu Glu Val Thr Ala Cys Trp Gln Pro His Ser
225                 230                 235                 240
Pro Arg Trp Xaa Ser Val Pro Pro Gln Pro Trp Cys Pro Leu Trp Pro
                245                 250                 255
Cys Leu Arg Ser Pro Ser Ala Cys His Cys Thr Val Gly Ala Ser Phe
            260                 265                 270
Trp Ala Gly Gln Gly Arg Ser Gln Leu Pro Gln Leu Ala Gly Arg Tyr
        275                 280                 285
Gly Gly Arg Asp Ala Gly Gly Asn Gln Gly Cys Ala Trp Arg Leu Arg
    290                 295                 300
Ala Ser Met Ser Ser Arg Trp Ala Trp Ala Arg Arg Ala Pro His Ser
305                 310                 315                 320
Gly Ser Glu Gly Leu Ser Thr Trp Ala Arg Gln Met Leu Cys Ser Thr
                325                 330                 335
Ser Ser Leu Gly Leu Ser Cys Leu Pro Arg Gly Ala Gly Leu Arg Glu
            340                 345                 350
Xaa Ala Ala Cys Pro Cys Leu Ser Pro Pro Pro Arg Arg Gly Phe Leu
        355                 360                 365
His Ser Pro Ser Phe Pro Asp Lys His His Pro Leu Ser Thr Val Pro
    370                 375                 380
Ser Pro Ile Asn His Pro Arg Val Glu Glu Cys Gly His Thr Ala Arg
385                 390                 395                 400
```

Asp Trp Gln Ala Val Pro Leu Ala Ala Leu Val Arg Asp Pro Leu Arg
405 410 415

Glu Ala Ser Trp Ala Pro Glu Ser Gly Gly Asp Leu Glu Asn Leu Tyr
420 425 430

Val
433

(2) INFORMATION FOR SEQ ID NO: 88:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 693 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 88:

CTTCCCCAAC TAATAAGGAC CCCCCTTTCA ACCCAAACAG TCCAAAAGGA CATAGACAAA 60
GGAGTAAACA ATGAACCAAA GAGTGCCAAT ATTCCCTGGT TATGCACCCT CCAAGCGGTG 120
GGAGAAGAAT TCGGCCCAGC CAGAGTGCAT GTACCTTTTT CTCTCTCACA CTTGAAGCAA 180
ATTAAAATAG ACNTAGGTNA ATTNTCAGAT AGCCCTGATG GYTATATTGA TGTTTTACAA 240
GGATTAGGAC AATCCTTTGA TCTGACATGG AGAGATATAA TATTACTGCT AAATCAGACG 300
CTAACCTCAA ATGAGAGAAG TGCTGCCATA ACTGGAGCCC GAGAGTTTGG CAATCTCTGG 360
TATCTCAGTC AGGTCAATGA TAGGATGACA ACGGAGGAAA GAGAACGATT CCCCACAGGG 420
CAGCAGGCAG TTCCCAGTGT AGCTCCTCAT TGGGACACAG AATCAGAACA TGGAGATTGG 480
TGCCGCAGAC ATTTACTAAC TTGCGTGCTA GAAGGACTAA GGAAAACTAG GAAGACTATG 540
AATTATTCAA TGATGTCCAC TATAACACAG GGGAAAGGAA GAAAATCCTA CTGCCTTTCT 600
GGAGAGACTA AGGGAGGCAT TGAGGAAGCA TACCAGGCAA GTGGACATTG GAGGCTCTGG 660
AAAAGGGAAA AGTTGGGCAA ATTGAATGCC TAA 693

(2) INFORMATION FOR SEQ ID NO: 89:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1577 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 89:

```
AACTTGCGTG CTAGAAGGAC TAAGGAAAAC TAGGAAGACT ATGAATTATT CAATGATGTC   60
CACTATAACA CAGGGGAAAG GAAGAAAATC CTACTGCCTT TCTGGAGAGA CTAAGGGAGG  120
CATTGAGGAA GCATACCAGG CAAGTGGACA TTGGAGGCTC TGGAAAAGGG AAAAGTTGGG  180
CAAATTGAAT GCCTAATAGG GCTTGCTTCC AGTGCAGTCT ACAAGGACGC TTTAGAAAAG  240
ATTGTCCAAG TAGAAATAAG CCGCCCCTCG TCCATGCCCC TTATGTCAAG GGAATCACTG  300
GAAGGCCTAC TGCCCCAGGG GACGAAGGTC CTCTGAGTCA GAAGCCACTA ACCTGATGAT  360
CCAGCAGCAG GACTGAGGGT GCCCGGGGCA AGTGCCAGCC CATGCCATCA CCCTCAGAGC  420
CCCGGGTATG TTTGACCATT GAGAGCCAGG AAGTTAACTG TCTCCTGGAC ACTGGCGCAG  480
CCTTCTCAGT CTTACTTTCC TGTCCCAGAC AATTGTCCTC CAGATCTGTC ACTATCCGAG  540
GGGTCCTAAG ACAGCCAGTC ACTACATACT TCTCTCAGCC ACTAAGTTGT GACTGGGGAA  600
CTTTACTCTT TTCACATGCT TTTCTAATTA TGCCTGAAAG CCCCACTCCC TTGTTAGGGA  660
GAGACATTTT AGCAAAAGCA GGGGCCATTA TACACCTGAA CATAGGAAAA GGAATACCCA  720
TTTGCTGTCC CCTGCTTGAG GAAGGAATTA ATCCTGAAGT CTGGGCAATA GAAGGACAAT  780
ATGGACAAGC AAAGAATGCC CGTCCTGTTC AAGTTAAACT AAAGGATTCT GCCTCCTTTC  840
CCTACCAAAG GAAGTACCCT CTTAGACCCG AGGCCCTACA AGGACTCAAA AGATTGTTAA  900
GGACCTAAAA GCCCAAGGCC TAGTAAAACC ATGCAGTAGC CCCTGCAATA CTCCAATTTT  960
AGGAGTAAGG AAACCCAACG GACAGTGGAG GTTAGTGCAA GATCTCAGGA TTATTAATGA 1020
GGCTGTTTTT CCTCTATACC CAGCTGTATC TAGCCCTTAT ACTCTGCTTT CCCTAATACC 1080
AGAGGAAGCA GAGTAGTTTA CAGTCCTGGA CCTTAAGGAT GCCTCTTTCT GCATCCCTGT 1140
ACATCCTGAT TCTCAATTCT TGTTTGTCTT TGAAGATCCT TTGAACCCAA TGTCTCAATT 1200
CACCTGGACT GTTTTACCCC AGGGGTTCCG GGATAGCCCC CATCTATTTG GCCAGGCATT 1260
AGCCCAAGAC TTGAGCCAAT TCTCATACCT GGACATCTTG TCCTTCGGTA TGGGATGATT 1320
TAATTTTAGC CACCCGTTCA GAAACCTTGT GCCATCAAGC CACCCAAGCG TTCTTAAATT 1380
TCCTCACTCC GTGTGGCTAC AAGGTTTCCA AACCAAAGGC TCAGCTCTGC TCACAGCAGG 1440
TTAAATACTT AGGGTTAAAA TTATCCAAAG GCACCAGGGC CCTCTGTGAG GAATGTATCC 1500
AACCTGTACT GGCTTATCTT CATCCCAAAA CCCTAAAGCA ACTAAGAAGG TCCTTGGCAT 1560
```

AACAGGTTTC TGCCGAA 1577

(2) INFORMATION FOR SEQ ID NO: 90:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 182 amino acids

(B) TYPE: amino acid

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 90:

```
Ser Ser Ser Arg Thr Glu Gly Ala Arg Gly Lys Cys Gln Pro Met Pro
1               5                   10                  15
Ser Pro Ser Glu Pro Arg Val Cys Leu Thr Ile Glu Ser Gln Glu Val
            20                  25                  30
Asn Cys Leu Leu Asp Thr Gly Ala Ala Phe Ser Val Leu Leu Ser Cys
        35                  40                  45
Pro Arg Gln Leu Ser Ser Arg Ser Val Thr Ile Arg Gly Val Leu Arg
    50                  55                  60
Gln Pro Val Thr Thr Tyr Phe Ser Gln Pro Leu Ser Cys Asp Trp Gly
65                  70                  75                  80
Thr Leu Leu Phe Ser His Ala Phe Leu Ile Met Pro Glu Ser Pro Thr
                85                  90                  95
Pro Leu Leu Gly Arg Asp Ile Leu Ala Lys Ala Gly Ala Ile Ile His
            100                 105                 110
Leu Asn Ile Gly Lys Gly Ile Pro Ile Cys Cys Pro Leu Leu Glu Glu
        115                 120                 125
Gly Ile Asn Pro Glu Val Trp Ala Ile Glu Gly Gln Tyr Gly Gln Ala
    130                 135                 140
Lys Asn Ala Arg Pro Val Gln Val Lys Leu Lys Asp Ser Ala Ser Phe
145                 150                 155                 160
Pro Tyr Gln Arg Lys Tyr Pro Leu Arg Pro Glu Ala Leu Gln Gly Leu
                165                 170                 175
Lys Arg Leu Leu Arg Thr
```

180

(2) INFORMATION FOR SEQ ID NO: 91:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 36 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 91:

AGATCTGCAG AATTCGATAT CACCCCCCCC CCCCCC 36

(2) INFORMATION FOR SEQ ID NO: 92:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 92:

AGATCTGCAG AATTCGATAT CA 22

(2) INFORMATION FOR SEQ ID NO: 93:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2304 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 93:

TCCAGCAGCA GGACTGAGGG TGCCCGGGGC AAGTGCCAGC CCATGCCATC 50
ACCCTCAGAG CCCCGGGTAT GTTTGACCAT TGAGAGCCAG GAAGTTAACT 100
GTCTCCTGGA CACTGGCGCA GCCTTCTCAG TCTTACTTTC CTGTCCCAGA 150
CAATTGTCCT CCAGATCTGT CACTATCCGA GGGGTCCTAG GACAGCCAGT 200
CACTACATAC TTCTCTCAGC CACTAAGTTG TGACTGGGGA ACTTTACTCT 250
TTTCACATGC TTTTCTAATT ATGCCTGAAA GCCCCACTCC CTTGTTAGGG 300
AGAGACATTT TAGCAAAAGC AGGGGCCATT ATACACCTGA ACATAGGAAA 350
AGGAATACCC ATTTGCTGTC CCCTGCTTGA GGAAGGAATT AATCCTGAAG 400
TCTGGGCAAT AGAAGGACAA TATGGACAAG CAAAGAATGC CCGTCCTGTT 450
CAAGTTAAAC TAAAGGATTC TGCCTCCTTT CCCTACCAAA GGAAGTACCC 500
TCTTAGACCC GAGGCCCTAC AAGGANCTCA AAAGATTGTT AAGGACCTAA 550
AAGCCCAAGG CCTAGTAAAA CCATGCAGTA GCCCCTGCAA TACTCCAATT 600
TTAGGAGTAA GGAAACCCAA CGGACAGTGG AGGTTAGTGC AAGATCTCAG 650
GATTATTAAT GAGGCTGTTT TTCCTCTATA CCCAGCTGTA TCTAGCCCTT 700
ATACTCTGCT TTCCCTAATA CCAGAGGAAG CAGAGTGGTT TACAGTCCTG 750
GACCTTAAGG ATGCCTTTTT CTGCATCCCT GTACGTCCTG ACTCTCAATT 800
CTTGTTTGCC TTTGAAGATC CTTTGAACCC AACGTCTCAA CTCACCTGGA 850
CTGTTTTACC CCAAGGGTTC AGGGATAGCC CCCATCTATT TGGCCAGGCA 900
TTAGCCCAAG ACTTGAGTCA ATTCTCATAC CTGGACACTC TTGTCCTTCA 950
GTACGTGGAT GATTTACTTT TAGTCGCCCG TTCAGAAACC TTGTGCCATC 1000
AAGCCACCCA AGAACTCTTA ACTTTCCTCA CTACCTGTGG CTACAAGGTT 1050
TCCAAACCAA AGGCTCGGCT CTGCTCACAG GAGATTAGAT ACTTAGGGCT 1100
AAAATTATCC AAAGGCACCA GGGCCCTCAG TGAGGAACGT ATCCAGCCTA 1150
TACTGGCTTA TCCTCATCCC AAAACCCTAA AGCAACTAAG AGGGTTCCTT 1200
GGCATAACAG GTTTCTGCCG AAAACAGATT CCCAGGTACA CCCCAATAGC 1250
CAGACCATTA TATACACTAA TTAGGGAAAC TCAGAAAGCC AATACCTATT 1300
TAGTAAGATG GACACCTACA GAAGTGGCTT TCCAGGCCCT AAAGAAGGCC 1350
CTAACCCAAG CCCCAGTGTT CAGCTTGCCA ACAGGGCAAG ATTTTTCTTT 1400
ATATGCCACA GAAAAAACAG GAATAGCTCT AGGAGTCCTT ACGCAGGTCT 1450
CAGGGATGAG CTTGCAACCC GTGGTATACC TGAGTAAGGA AATTGATGTA 1500
GTGGCAAAGG GTTGGCCTCA TTGTTTATGG GTAATGGCGG CAGTAGCAGT 1550
CTTAGTATCT GAAGCAGTTA AAATAATACA GGGAAGAGAT CTTACTGTGT 1600

GGACATCTCA TGATGTGAAC GGCATACTCA CTGCTAAAGG AGACTTGTGG 1650
TTGTCAGACA ACCATTTACT TAATTATCAG GCTCTATTAC TTGAAGAGCC 1700
AGTGCTGAGA CTGCGCACTT GTGCAACTCT TAAACCCGCC ACATTTCTTC 1750
CAGACAATGA AGAAAAGATA GAACATAACT GTCAACAAGT AATTGCTCAA 1800
ACCTATGCTG CTCGAGGGGA CCTTCTAGAG GTTCCCTTGA CTGATCCCGA 1850
CCTCAACTTG TATACTGATG GAAGTTCCTT GGCAGAAAAA GGACTTCGAA 1900
AAGCGGGGTA TGCAGTGATC AGTGATAATG GAATACTTGA AAGTAATCGC 1950
CTCACTCCAG GAACTAGTGC TCACCTGGCA GAACTAATAG CCCTCACTTG 2000
GGCACTAGAA TTAGGAGAAG GAAAAAGGGT AAATATATAT TCAGACTCTA 2050
AGTATGCTTA CCTAGTCCTC CATGCCCATG CAGCAATATG GAGAGAGAGG 2100
GAATTCCTAA CTTCTGAGGG AACACCTATC AACCATCAGG AAGCCATTAG 2150
GAGATTATTA TTGGCTGTAC AGAAACCTAA AGAGGTGGCA GTCTTACACT 2200
GCCAGGGTCA TCAGGAAGAA GAGGAAAGGG AAATAGAAGG CAATCGCCAA 2250
GCGGATATTG AAGCAAAAAA AGCCGCAAGG CAGGACTCTC CATTAGAAAT 2300
GCTT 2304

(2) INFORMATION FOR SEQ ID NO: 94:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 2364 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 94:

ATGATCCAGC AGCAGGACNG AGGGTGCCCG GGGCAAGCGC CAGCCCATGC 50
CATCACCCTC ACAGAGCCCC AGGTATGCTT GACCATTGAG GGTCAGAAGG 100
GTNACTGTCT CCTGGACACT GGCGGNGCCT TCTCAGTCTT ACTTTCCTGT 150
CCTGGACAAC TGTCCTCCAG ATCTGTCACT GTCCGAGGGG TCCTAGGACA 200
GCCAGTCACT AGATACTTCT CCCAGCCACT AAGTTGTGAC TGGGGAACTT 250
TACTCTTCCC ACATGCTTTT CTAATTATGC CTGAAAGCCC CACTCTCTTG 300
TTGGGGAGAG ACATTCTAGC AAAAGCAGGG GCCATTATAC ATGTGAATAT 350
AGGAGAAGGA ACAACTGTTT GTTGTCCCCT GCTTGAGGAA GGAATTAATC 400
CTGAAGTCCG GGCAACAGAA GGACAATATG GACAAGCAAA GAATGCCCGT 450
CCTGTTCAAG TTAAACTAAA GGATTCCACC TCCTTTCCCT ACCAAAGGCA 500
GTACCCCCTC AGACCCGAGA CCCAACAAGA ACTCCAAAAG ATTGTAAAGG 550
ACCTAAAAGC CCAAGGCCTA GTAAAACCAA GCAATAGCCC TTGCAAGACT 600

```
CCAATTTTAG GAGTAAGGAA ACCCAACGGA CAGTGGAGGT TAGTGCAAGA    650
ACTCAGGATT ATCAATGAGG CTGTTGTTCC TCTATACCCA GCTGTACCTA    700
ACCCTTATAC AGTGCTTTCC CAAATACCAG AGGAAGCAGA GTGGTTTACA    750
GTCCTGGACC TTAAGGATGC CTTTTTCTGC ATCCCTGTAC GTCCTGACTC    800
TCAATTCTTG TTTGCCTTTG AAGATCCTTT GAACCCAACG TCTCAACTCA    850
CCTGGACTGT TTTACCCCAA GGGTTCAGGG ATAGCCCCCA TCTATTTGGC    900
CAGGCATTAG CCCAAGACTT GAGTCAATTC TCATACCTGG ACACTCTTGT    950
CCTTCAGTAC ATGGATGATT TACTTTTAGT CGCCCGTTCA GAAACCTTGT   1000
GCCATCAAGC CACCCAAGAA CTCTTAACTT TCCTCACTAC CTGTGGCTAC   1050
AAGGTTTCCA AACCAAAGGC TCGGCTCTGC TCACAGGAGA TTAGATACTN   1100
AGGGCTAAAA TTATCCAAAG GCACCAGGGC CCTCAGTGAG GAACGTATCC   1150
AGCCTATACT GGCTTATCCT CATCCCAAAA CCCTAAAGCA ACTAAGAGGG   1200
TTCCTTGGCA TAACAGGTTT CTGCCGAAAA CAGATTCCCA GGTACASCCC   1250
AATAGCCAGA CCATTATATA CACTAATTAN GGAAACTCAG AAAGCCAATA   1300
CCTATTTAGT AAGATGGACA CCTACAGAAG TGGCTTTCCA GGCCCTAAAG   1350
AAGGCCCTAA CCCAAGCCCC AGTGTTCAGC TTGCCAACAG GGCAAGATTT   1400
TTCTTTATAT GCCACAGAAA AAACAGGAAT AGCTCTAGGA GTCCTTACGC   1450
AGGTCTCAGG GATGAGCTTG CAACCCGTGG TATACCTGAG TAAGGAAATT   1500
GATGTAGTGG CAAAGGGTTG GCCTCATNGT TTATGGGTAA TGGNGGCAGT   1550
AGCAGTCTNA GTATCTGAAG CAGTTAAAAT AATACAGGGA AGAGATCTTN   1600
CTGTGTGGAC ATCTCATGAT GTGAACGGCA TACTSRCTGC TAAAGGAGAC   1650
TTGTGGTTGT CAGACAACCA TTTACTTAAN TAYCAGGCYY TATTACTTGA   1700
AGAGCCAGTG CTGNGACTGC GCACTTGTCC AACTCTTAAA CCCAAACTTA   1750
TGCTGCCCAG AAGGATCTTT NTAGAGGTCC CCTTAGCCAA CCCTGACCTC   1800
AACTATATAT ATACTGATGG AAGTTCGTTT GTAGAAAAGG GATTACAAAG   1850
GGNAGGATAT NCCATAGGTG TTAGTGATAA AGCAGTACTT GAAAGTAAGC   1900
CTCTTCCCCC CCAGGGACCA GCGCCCCCGT TAGCAGAACT AGTGGCACTG   1950
ACCCCGCGAG CCTTAGAACT TTGGAAAGGG AGGAGGATAA ATGTGTATAC   2000
AGATAGCAAG TATGCTTATC TAATCCGAAA TGCCCATGTT GCAATATGGA   2050
AAGAAAGGGA GTTCCTAACC TCTGGGGGAA CCCCCATTAA ATACCACAAG   2100
TTAATCATGG AGTTATTGCA CACAGTGCAA AAACTCAAGG AGGTGGAAGT   2150
CTTACACTGC CAAAGCCATC AGAAAAGGGA AAGAGGGGAA GAGCAGCATA   2200
AGTGGCTACA GAGGCAAGGA AAGACTAGCA GAAAGGAAAG AGAGAAAGAG   2250
ACAGAAAGTC AGAGAGAGAG AGAGGAAGAG ACAGAGCACA AAGAGGGAGT   2300
CAGAGAGAGA GAGAGACAGA GAGTCAGAGA GAAGGAAAGA GAGAGAGGAA   2350
GAGACAAAGA ATGAH                                         2365
```

(2) INFORMATION FOR SEQ ID NO: 95:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 768 amino acids

(B) TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 95:

```
SSSRTEGARG KCQPMPSPSE PRVCLTIESQ EVNCLLDTGA AFSVLLSCPR    50
QLSSRSVTIR GVLGQPVTTY FSQPLSCDWG TLLFSHAFLI MPESPTPLLG   100
RDILAKAGAI IHLNIGKGIP ICCPLLEEGI NPEVWAIEGQ YGQAKNARPV   150
QVKLKDSASF PYQRKYPLRP EALQGXQKIV KDLKAQGLVK PCSSPCNTPI   200
LGVRKPNGQW RLVQDLRIIN EAVFPLYPAV SSPYTLLSLI PEEAEWFTVL   250
DLKDAFFCIP VRPDSQFLFA FEDPLNPTSQ LTWTVLPQGF RDSPHLFGQA   300
LAQDLSQFSY LDTLVLQYVD DLLLVARSET LCHQATQELL TFLTTCGYKV   350
SKPKARLCSQ EIRYLGLKLS KGTRALSEER IQPILAYPHP KTLKQLRGFL   400
GITGFCRKQI PRYTPIARPL YTLIRETQKA NTYLVRWTPT EVAFQALKKA   450
LTQAPVFSLP TGQDFSLYAT EKTGIALGVL TQVSGMSLQP VVYLSKEIDV   500
VAKGWPHCLW VMAAVAVLVS EAVKIIQGRD LTVWTSHDVN GILTAKGDLW   550
LSDNHLLNYQ ALLLEEPVLR LRTCATLKPA TFLPDNEEKI EHNCQQVIAQ   600
TYAARGDLLE VPLTDPDLNL YTDGSSLAEK GLRKAGYAVI SDNGILESNR   650
LTPGTSAHLA ELIALTWALE LGEGKRVNIY SDSKYAYLVL HAHAAIWRER   700
EFLTSEGTPI NHQEAIRRLL LAVQKPKEVA VLHCQGHQEE EEREIEGNRQ   750
ADIEAKKAAR QDSPLEML                                      768
```

(2) INFORMATION FOR SEQ ID NO: 96:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 114 amino acids

(B) TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 96:

```
SSSRTEGARG KCQPMPSPSE PRVCLTIESQ EVNCLLDTGA AFSVLLSCPR    50
QLSSRSVTIR GVLGQPVTTY FSQPLSCDWG TLLFSHAFLI MPESPTPLLG   100
RDILAKAGAI IHLN                                          114
```

(2) INFORMATION FOR SEQ ID NO: 97:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: amino acids

(B) TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 97:

IGKGIPICCPLLEEGINPEVWAIEGQYGQAKNARPV
QVKLKDSASFPYQRKYPLRPEALQGXQKIVKDLKAQGLVKPCSSPCNTPI
LGVRKPNGQWRLVQDLRIINEAVFPLYPAVSSPYTLLSLIPEEAEWFTVL
DLKDAFFCIPVRPDSQFLFAFEDPLNPTSQLTWTVLPQGFRDSPHLFGQA
LAQDLSQFSYLDTLVLQYVDDLLLVARSETLCHQATQELLTFLTTCGYKV
SKPKARLCSQEIRYLGLKLSKGTRALSEERIQPILAYPHPKTLKQLRGFL
GITGFCRKQIPRYTPIARPLYTLIRETQKANTYLVRWTPTEVAFQALKKA
LTQAPVFSLPTGQDFSLYATEKTGIALGVLTQVSGMSLQPVVYLSKEIDV
VAKGWPHCLWVMAAVAVLVSEAVKIIQGRDLTVWTSHDVNGILTAKGDLW
LSDNHLLNYQALLLEEPVLRLRTCATLKPATFLPDNEEKIEHNCQQVIAQ
TYAARGDLLEVPLTDPDLNLYTDGSSLAEKGLRKAGYAVISDNGILESNR
LTPGTSAHLAELIALTWALELGEGKRVNIYSDSKYAYLVLHAHAAIWRER
EFLTSEGTPINHQEAIRRLLLAVQKPKEVAVLHCQGHQEEEEREIEGNRQ
ADIEAKKAARQDSPLEML

(2) INFORMATION FOR SEQ ID NO: 98:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: amino acids

(B) TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 98:

LYTDGSSLAEKGLRKAGYAVISDNGILESNR
LTPGTSAHLAELIALTWALELGEGKRVNIYSDSKYAYLVLHAHAAIWRER
EFLTSEGTPINHQEAIRRLLLAVQKPKEVAVLHCQGHQEEEEREIEGNRQ
ADIEAKKAARQDSPLEML

(2) INFORMATION FOR SEQ ID NO: 99

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 99:

AGGAGTAAGG AAACCCAACG GAC 23

(2) INFORMATION FOR SEQ ID NO: 100

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 100:

TAAGAGTTGC ACAAGTGCG 19

(2) INFORMATION FOR SEQ ID NO: 101

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 101:

TCAGGGATAG CCCCCATCTA T 21

(2) INFORMATION FOR SEQ ID NO: 102

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 102:

AACCCTTTGC CACTACATCA ATTT 24

(2) INFORMATION FOR SEQ ID NO: 103

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 103:

AGCAGCAGGA CTGAGGGT 18

(2) INFORMATION FOR SEQ ID NO: 104

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 104:

CTGTCCGTTG GGTTTCCTTA CTCCT 25

(2) INFORMATION FOR SEQ ID NO: 105

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 105:

GACAGCAAAT GGGTATTCCT TTCC 24

(2) INFORMATION FOR SEQ ID NO: 106

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 106:

AGGAGTAAGG AAACCCAACG GACA 24

(2) INFORMATION FOR SEQ ID NO: 107

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 107:

TGTATATAAT GGTCTGGCTA TTGGG 25

(2) INFORMATION FOR SEQ ID NO: 108

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 108:

TTCGGCAGAA ACCTGTTATG CCAAGG 26

(2) INFORMATION FOR SEQ ID NO: 109

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 109:

GGCTCTGCTC ACAGGAGATT AGATAC 26

(2) INFORMATION FOR SEQ ID NO: 110

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 110:

AAAGGCACCA GGGCCCTCAG TGAGGA 26

(2) INFORMATION FOR SEQ ID NO: 111

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 111:

GGTTTAAGAG TTGCACAAGT GCGCAGTC 28

(2) INFORMATION FOR SEQ ID NO: 112:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 310 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 112:

GCTTATAGAA GGACCCCTAG TATGGGGTAA TCCCCTCTGG GAAACCAAGC CCCAGTACTC 60

AGCAGGAAAA ATAGAATAGG AAACCTCACA AGGACATACT TTCCTCCCCT CCAGATGGCT 120

AGCCACTGAG GAAGGAAAAA TACTTTCACC TGCAGCTAAC CAACAGAAAT TACTTAAAAC 180

CCTTCACCAA ACCTTCCACT TAGGCATTGA TAGCACCCAT CAGATGGCCA AATTATTATT 240

TACTGGACCA GGCCTTTTCA AAACTATCAA GAAGATAGTC AGGGGCTGTG AAGTGTGCCA 300

AAGAAATAAT 310

(2) INFORMATION FOR SEQ ID NO: 113:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 103 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 113:

Leu Ile Glu Gly Pro Leu Val Trp Gly Asn Pro Leu Trp Glu Thr Lys
1   5   10   15

Pro Gln Tyr Ser Ala Gly Lys Ile Glu Xaa Glu Thr Ser Gln Gly His
            20   25   30

Thr Phe Leu Pro Ser Arg Trp Leu Ala Thr Glu Glu Gly Lys Ile Leu
        35   40   45

Ser Pro Ala Ala Asn Gln Gln Lys Leu Leu Lys Thr Leu His Gln Thr
    50   55   60

Phe His Leu Gly Ile Asp Ser Thr His Gln Met Ala Lys Leu Leu Phe

65 70 75 80

Thr Gly Pro Gly Leu Phe Lys Thr Ile Lys Lys Ile Val Arg Gly Cys

85 90 95

Glu Val Cys Gln Arg Asn Asn

100

(2) INFORMATION FOR SEQ ID NO: 114:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 635 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 114:

```
CCCTGTATCT TTAACCTCCT TGTTAAGTTT GTCTCTTCCA GAATCAAAAC TGTAAAACTA   60
CAAATTGTTC TTCAAATGGA GCACCAGATG GAGTCCATGA CTAAGATCCA CCGTGGACCC  120
CTGGACCGGC CTGCTAGCCC ATGCTCCGAT GTTAATGACA TTGAAGGCAC CCCTCCCGAG  180
GAAATCTCAA CTGCACAACC CCTACTATGC CCCAATTCAG CGGGAAGCAG TTAGAGCGGT  240
CATCAGCCAA CCTCCCCAAC AGCACTTGGG TTTTCCTGTT GAGAGGGGGG ACTGAGAGAC  300
AGGACTAGCT GGATTTCCTA GGCCAACGAA GAATCCCTAA GCCTAGCTGG GAAGGTGACT  360
GCATCCACCT CTAAACATGG GGCTTGCAAC TTAGCTCACA CCCGACCAAT CAGAGAGCTC  420
ACTAAAATGC TAATTAGGCA AAAATAGGAG GTAAAGAAAT AGCCAATCAT CTATTGCCTG  480
AGAGCACAGC GGGAGGGACA AGGATCGGGA TATAAACCCA GGCATTCGAG CCGGCAACGG  540
CAACCCCCTT TGGGTCCCCT CCCTTTGTAT GGGCGCTCTG TTTTCACTCT ATTTCACTCT  600
ATTAAATCTT GCAACTGAAA AAAAAAAAAA AAAAA                              635
```

(2) INFORMATION FOR SEQ ID NO: 115:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 77 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 115:

Pro Cys Ile Phe Asn Leu Leu Val Lys Phe Val Ser Ser Arg Ile Lys

1 5 10 15

Thr Val Lys Leu Gln Ile Val Leu Gln Met Glu His Gln Met Glu Ser
20 25 30
Met Thr Lys Ile His Arg Gly Pro Leu Asp Arg Pro Ala Ser Pro Cys
35 40 45
Ser Asp Val Asn Asp Ile Glu Gly Thr Pro Pro Glu Glu Ile Ser Thr
50 55 60
Ala Gln Pro Leu Leu Cys Pro Asn Ser Ala Gly Ser Ser
65 70 75

(2) INFORMATION FOR SEQ ID NO: 116:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 32 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 116:

TGGGGTTCCA TTTGTAAGAC CATCTGTAGC TT 32

(2) INFORMATION FOR SEQ ID NO: 117:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1481 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 117:

ATGGCCCTCC CTTATCATAC TTTTCTCTTT ACTGTTCTCT TACCCCCTTT CGCTCTCACT 60
GCACCCCCTC CATGCTGCTG TACAACCAGT AGCTCCCCTT ACCAAGAGTT TCTATGAAGA 120
ACGCGGCTTC CTGGAAATAT TGATGCCCCA TCATATAGGA GTTTATCTAA GGGAAACTCC 180
ACCTTCACTG CCCACACCCA TATGCCCCGC AACTGCTATA ACTCTGCCAC TCTTTGCATG 240
CATGCAAATA CTCATTATTG GACAGGGAAA ATGATTAATC CTAGTTGTCC TGGAGGACTT 300
GGAGCCACTG TCTGTTGGAC TTACTTCACC CATACCAGTA TGTCTGATGG GGGTGGAATT 360
CAAGGTCAGG CAAGAGAAAA ACAAGTAAAG GAAGCAATCT CCCAACTGAC CCGGGGACAT 420
AGCACCCCTA GCCCCTACAA AGGACTAGTT CTCTCAAAAC TACATGAAAC CCTCCGTACC 480
CATACTCGCC TGGTGAGCCT ATTTAATACC ACCCTCACTC GGCTCCATGA GGTCTCAGCC 540

CAAAACCCTA CTAACTGTTG GATGTGCCTC CCCCTGCACT TCAGGCCATA CATTTCAATC 600
CCTGTTCCTG AACAATGGAA CAACTTCAGC ACAGAAATAA ACACCACTTC CGTTTTAGTA 660
GGACCTCTTG TTTCCAATCT GGAAATAACC CATACCTCAA ACCTCACCTG TGTAAAATTT 720
AGCAATACTA TAGACACAAC CAGCTCCCAA TGCATCAGGT GGGTAACACC TCCCACACGA 780
ATAGTCTGCC TACCCTCAGG AATATTTTTT GTCTGTGGTA CCTCAGCCTA TCATTGTTTG 840
AATGGCTCTT CAGAATCTAT GTGCTTCCTC TCATTCTTAG TGCCCCCTAT GACCATCTAC 900
ACTGAACAAG ATTTATACAA TCATGTCGTA CCTAAGCCCC ACAACAAAAG AGTACCCATT 960
CTTCCTTTTG TTATCAGAGC AGGAGTGCTA GGCAGACTAG GTACTGGCAT TGGCAGTATC 1020
ACAACCTCTA CTCAGTTCTA CTACAAACTA TCTCAAGAAA TAAATGGTGA CATGGAACAG 1080
GTCACTGACT CCCTGGTCAC CTTGCAAGAT CAACTTAACT CCCTAGCAGC AGTAGTCCTT 1140
CAAAATCGAA GAGCTTTAGA CTTGCTAACC GCCAAAAGAG GGGGAACCTG TTTATTTTTA 1200
GGAGAAGAAC GCTGTTATTA TGTTAATCAA TCCAGAATTG TCACTGAGAA AGTTAAAGAA 1260
ATTCGAGATC GAATACAATG TAGAGCAGAG GAGCTTCAAA ACACCGAACG CTGGGGCCTC 1320
CTCAGCCAAT GGATGCCCTG GGTTCTCCCC TTCTTAGGAC CTCTAGCAGC TCTAATATTG 1380
TTACTCCTCT TTGGACCCTG TATCTTTAAC CTCCTTGTTA AGTTTGTCTC TTCCAGAATT 1440
GAAGCTGTAA AGCTACAGAT GGTCTTACAA ATGGAACCCC A 1481

(2) INFORMATION FOR SEQ ID NO: 118:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 493 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 118:

Met Ala Leu Pro Tyr His Thr Phe Leu Phe Thr Val Leu Leu Pro Pro
1 5 10 15
Phe Ala Leu Thr Ala Pro Pro Pro Cys Cys Cys Thr Thr Ser Ser Ser
20 25 30
Pro Tyr Gln Glu Phe Leu Xaa Arg Thr Arg Leu Pro Gly Asn Ile Asp
35 40 45
Ala Pro Ser Tyr Arg Ser Leu Ser Lys Gly Asn Ser Thr Phe Thr Ala
50 55 60
His Thr His Met Pro Arg Asn Cys Tyr Asn Ser Ala Thr Leu Cys Met
65 70 75 80
His Ala Asn Thr His Tyr Trp Thr Gly Lys Met Ile Asn Pro Ser Cys

85 90 95

Pro Gly Gly Leu Gly Ala Thr Val Cys Trp Thr Tyr Phe Thr His Thr

100 105 110

Ser Met Ser Asp Gly Gly Gly Ile Gln Gly Gln Ala Arg Glu Lys Gln

115 120 125

Val Lys Glu Ala Ile Ser Gln Leu Thr Arg Gly His Ser Thr Pro Ser

130 135 140

Pro Tyr Lys Gly Leu Val Leu Ser Lys Leu His Glu Thr Leu Arg Thr

145 150 155 160

His Thr Arg Leu Val Ser Leu Phe Asn Thr Thr Leu Thr Arg Leu His

165 170 175

Glu Val Ser Ala Gln Asn Pro Thr Asn Cys Trp Met Cys Leu Pro Leu

180 185 190

His Phe Arg Pro Tyr Ile Ser Ile Pro Val Pro Glu Gln Trp Asn Asn

195 200 205

Phe Ser Thr Glu Ile Asn Thr Thr Ser Val Leu Val Gly Pro Leu Val

210 215 220

Ser Asn Leu Glu Ile Thr His Thr Ser Asn Leu Thr Cys Val Lys Phe

225 230 235 240

Ser Asn Thr Ile Asp Thr Thr Ser Ser Gln Cys Ile Arg Trp Val Thr

245 250 255

Pro Pro Thr Arg Ile Val Cys Leu Pro Ser Gly Ile Phe Phe Val Cys

260 265 270

Gly Thr Ser Ala Tyr His Cys Leu Asn Gly Ser Ser Glu Ser Met Cys

275 280 285

Phe Leu Ser Phe Leu Val Pro Pro Met Thr Ile Tyr Thr Glu Gln Asp

290 295 300

Leu Tyr Asn His Val Val Pro Lys Pro His Asn Lys Arg Val Pro Ile

305 310 315 320

Leu Pro Phe Val Ile Arg Ala Gly Val Leu Gly Arg Leu Gly Thr Gly

325 330 335

Ile Gly Ser Ile Thr Thr Ser Thr Gln Phe Tyr Tyr Lys Leu Ser Gln

340 345 350

Glu Ile Asn Gly Asp Met Glu Gln Val Thr Asp Ser Leu Val Thr Leu

355 360 365

Gln Asp Gln Leu Asn Ser Leu Ala Ala Val Val Leu Gln Asn Arg Arg

370 375 380

Ala Leu Asp Leu Leu Thr Ala Lys Arg Gly Gly Thr Cys Leu Phe Leu
385 390 395 400

Gly Glu Glu Arg Cys Tyr Tyr Val Asn Gln Ser Arg Ile Val Thr Glu
405 410 415

Lys Val Lys Glu Ile Arg Asp Arg Ile Gln Cys Arg Ala Glu Glu Leu
420 425 430

Gln Asn Thr Glu Arg Trp Gly Leu Leu Ser Gln Trp Met Pro Trp Val
435 440 445

Leu Pro Phe Leu Gly Pro Leu Ala Ala Leu Ile Leu Leu Leu Leu Phe
450 455 460

Gly Pro Cys Ile Phe Asn Leu Leu Val Lys Phe Val Ser Ser Arg Ile
465 470 475 480

Glu Ala Val Lys Leu Gln Met Val Leu Gln Met Glu Pro
485 490

(2) INFORMATION FOR SEQ ID NO: 119:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 32 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 119:

TCAAAATCGA AGAGCTTTAG ACTTGCTAAC CG 32

(2) INFORMATION FOR SEQ ID NO: 120:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1329 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 120:

TCAAAATCGA AGAGCTTTAG ACTTGCTAAC CGCCAAAAGA GGGGGAACCT GTTTATTTTT 60
AGGGGAAGAA TGCTGTTAGT ATGTTAATCA ATCTGGAATC ATTACTGAGA AAGTTAAAGA 120

AATTTGAGAT CGAATATAAT GTAGAGCAGA GGACCTTCAA AACACTGCAC CCTGGGGCCT 180
CCTCAGCCAA TGGATGCCCT GGACTCTCCC CTTCTTAGGA CCTCTAGCAG CTATAATATT 240
TTTACTCCTC TTTGGACCCT GTATCTTCAA CTTCCTTGTT AAGTTTGTCT CTTCCAGAAT 300
TGAAGCTGTA AAGCTACAAA TAGTTCTTCA AATGGAACCC CAGATGCAGT CCATGACTAA 360
AATCTACCGT GGACCCCTGG ACCGGCCTGC TAGACTATGC TCTGATGTTA ATGACATTGA 420
AGTCACCCCT CCCGAGGAAA TCTCAACTGC ACAACCCCTA CTACACTCCA ATTCAGTAGG 480
AAGCAGTTAG AGCAGTTGTC AGCCAACCTC CCCAACAGTA CTTGGGTTTT CCTGTTGAGA 540
GGGTGGACTG AGAGACAGGA CTAGCTGGAT TTCCTAGGCT GACTAAGAAT CCCNAAGCCT 600
ANCTGGGAAG GTGACCGCAT CCATCTTTAA ACATGGGGCT TGCAACTTAG CTCACACCCG 660
ACCAATCAGA GAGCTCACTA AAATGCTAAT CAGGCAAAAA CAGGAGGTAA AGCAATAGCC 720
AATCATCTAT TGCCTGAGAG CACAGCGGGA AGGACAAGGA TTGGGATATA AACTCAGGCA 780
TTCAAGCCAG CAACAGCAAC CCCCTTTGGG TCCCCTCCCA TTGTATGGGA GCTCTGTTTT 840
CACTCTATTT CACTCTATTA AATCATGCAA CTGCACTCTT CTGGTCCGTG TTTTTTATGG 900
CTCAAGCTGA GCTTTTGTTC GCCATCCACC ACTGCTGTTT GCCACCGTCA CAGACCCGCT 960
GCTGACTTCC ATCCCTTTGG ATCCAGCAGA GTGTCCACTG TGCTCCTGAT CCAGCGAGGT 1020
ACCCATTGCC ACTCCCGATC AGGCTAAAGG CTTGCCATTG TTCCTGCATG GCTAAGTGCC 1080
TGGGTTTGTC CTAATAGAAC TGAACACTGG TCACTGGGTT CCATGGTTCT CTTCCATGAC 1140
CCACGGCTTC TAATAGAGCT ATAACACTCA CCGCATGGCC CAAGATTCCA TTCCTTGGTA 1200
TCTGTGAGGC CAAGAACCCC AGGTCAGAGA ANGTGAGGCT TGCCACCATT TGGGAAGTGG 1260
CCCACTGCCA TTTTGGTAGC GGCCCACCAC CATCTTGGGA GCTGTGGGAG CAAGGATCCC 1320
CCAGTAACA 1329

(2) INFORMATION FOR SEQ ID NO: 121:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 162 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 121:

Gln Asn Arg Arg Ala Leu Asp Leu Leu Thr Ala Lys Arg Gly Gly Thr
1 5 10 15
Cys Leu Phe Leu Gly Glu Glu Cys Cys Xaa Tyr Val Asn Gln Ser Gly
20 25 30
Ile Ile Thr Glu Lys Val Lys Glu Ile Xaa Asp Arg Ile Xaa Cys Arg
35 40 45

Ala Glu Asp Leu Gln Asn Thr Ala Pro Trp Gly Leu Leu Ser Gln Trp
50 55 60

Met Pro Trp Thr Leu Pro Phe Leu Gly Pro Leu Ala Ala Ile Ile Phe
65 70 75 80

Leu Leu Leu Phe Gly Pro Cys Ile Phe Asn Phe Leu Val Lys Phe Val
85 90 95

Ser Ser Arg Ile Glu Ala Val Lys Leu Gln Ile Val Leu Gln Met Glu
100 105 110

Pro Gln Met Gln Ser Met Thr Lys Ile Tyr Arg Gly Pro Leu Asp Arg
115 120 125

Pro Ala Arg Leu Cys Ser Asp Val Asn Asp Ile Glu Val Thr Pro Pro
130 135 140

Glu Glu Ile Ser Thr Ala Gln Pro Leu Leu His Ser Asn Ser Val Gly
145 150 155 160

Ser Ser

(2) INFORMATION FOR SEQ ID NO: 122:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 122:

GGCATTGATA GCACCCATCA G 21

(2) INFORMATION FOR SEQ ID NO: 123:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 123:

CATGTCACCA GGGTGGAATA G 21

(2) INFORMATION FOR SEQ ID NO: 124:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 758 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 124:

```
GGCATTGATA GCACCCATCA GATGGCCAAA TCATTATTTA CTGGACCAGG CCTTTTCAAA   60
ACTATCAAGC AGATAGGGCC CGTGAAGCAT GCCAAAGAAA TAATCCCCTG CCTTATCGCC  120
ATGTTCCTTC AGGAGAACAA AGAACAGGCC ATTACCCAGG GGAAGACTGG CAACTAGATT  180
TTACCCACAT GGCCAAATGT CAGGGATTTC AGCATCTACT AGTCTGGGCA GATACTTTCA  240
CTGGTTGGGT GGAGTCTTCT CCTTGTAGGA CAGAAAAGAC CCAAGAGGTA ATAAAGGCAC  300
TAATGAAATA ATTCCCAGAT TTGGACTTCC CCCAGGATTA CAGGGTGACA ATGGCCCCGC  360
TTTCAAGGCT GCAGTAACCC AGGGAGTATC CCAGGTGTTA GGCATACAAT ATCACTTACA  420
CTGTGCCTGG AGGCCACAAT CCTCCAGAAA AGTCAAGAAA ATGAATGAAA CACTCAAAGA  480
TCTAAAAAAG CTAACCCAAG AAACCCACAT TGCATGACCT GTTCTGTTGC CTATAACCTT  540
ACTAAGAATC CATAACTATC CCCCAAAAAG CAGGACTTAG CCCATACGAG ATGCTATATG  600
GATGGCCTTT CCTAACCAAT GACCTTGTGC TTGACTGAGA AATGGCCAAC TTAGTTGCAG  660
ACATCACCTC CTTAGCCAAA TATCAACAAG TTCTTAAAAC ATCACAGGGA ACCTGTCCCC  720
GAGAGGAGGG AAAGGAACTA TTCCACCCTG GTGACATG                          758
```

(2) INFORMATION FOR SEQ ID NO: 126:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 126:

```
CGGACATCCA AAGTGATGGG AAACG                                         25
```

(2) INFORMATION FOR SEQ ID NO: 127:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 127:

GGACAGGAAA GTAAGACTGA GAAGGC 26

(2) INFORMATION FOR SEQ ID NO: 128:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 128:

CCTAGAACGT ATTCTGGAGA ATTGGG 26

(2) INFORMATION FOR SEQ ID NO: 129:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 129:

TGGCTCTCAA TGGTCAAACA TACCCG 26

(2) INFORMATION FOR SEQ ID NO: 130:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1511 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 130:

CCTAGAACGT ATTCTGGAGA ATTGGGACCA ATGTGACACT CAGACGCTAA GAAAGAAACG 60

```
ATTTATATTC TTCTGCAGTA CCGCCTGGCC ACAATATCCT CTTCAAGGGA GAGAAACCTG  120
GCTTCCTGAG GGAAGTATAA ATTATAACAT CATCTTACAG CTAGACCTCT TCTGTAGAAA  180
GGAGGGCAAA TGGAGTGAAG TGCCATATGT GCAAACTTTC TTTTCATTAA GAGACAACTC  240
ACAATTATGT AAAAAGTGTG GTTTATGCCC TACAGGAAGC CCTCAGAGTC CACCTCCCTA  300
CCCCAGCGTC CCCTCCCCGA CTCCTTCCTC AACTAATAAG GACCCCCCTT TAACCCAAAC  360
GGTCCAAAAG GAGATAGACA AAGGGGTAAA CAATGAACCA AAGAGTGCCA ATATTCCCCG  420
ATTATGCCCC CTCCAAGCAG TGAGAGGAGG AGAATTCGGC CCAGCCAGAG TGCCTGTACC  480
TTTTTCTCTC TCAGACTTAA AGCAAATTAA AATAGACCTA GGTAAATTCT CAGATAACCC  540
TGACGGCTAT ATTGATGTTT TACAAGGGTT AGGACAATCC TTTGATCTGA CATGGAGAGA  600
TATAATGTTA CTACTAAATC AGACACTAAC CCCAAATGAG AGAAGTGCCG CTGTAACTGC  660
AGCCCGAGAG TTTGGCGATC TTTGGTATCT CAGTCAGGCC AACAATAGGA TGACAACAGA  720
GGAAAGAACA ACTCCCACAG GCCAGCAGGC AGTTCCCAGT GTAGACCCTC ATTGGGACAC  780
AGAATCAGAA CATGGAGATT GGTGCCACAA ACATTTGCTA ACTTGCGTGC TAGAAGGACT  840
GAGGAAAACT AGGAAGAAGC CTATGAATTA CTCAATGATG TCCACTATAA CACAGGGAAA  900
GGAAGAAAAT CTTACTGCTT TTCTGGACAG ACTAAGGGAG GCATTGAGGA AGCATACCTC  960
CCTGTCACCT GACTCTATTG AAGGCCAACT AATCTTAAAG GATAAGTTTA TCACTCAGTC 1020
AGCTGCAGAC ATTAGAAAAA ACTTCAAAAG TCTGCCTTAG GCCCGGAGCA GAACTTAGAA 1080
ACCCTATTTA ACTTGGCATC CTCAGTTTTT TATAATAGAG ATCAGGAGGA GCAGGCGAAA 1140
CGGGACAAAC GGGATAAAAA AAAAAGGGGG GGTCCACTAC TTTAGTCATG GCCCTCAGGC 1200
AAGCAGACTT TGGAGGCTCT GCAAAAGGGA AAAGCTGGGC AAATCAAATG CCTAATAGGG 1260
CTGGCTTCCA GTGCGGTCTA CAAGGACACT TTAAAAAAGA TTATCCAAGT AGAAATAAGC 1320
CGCCCCCTTG TCCATGCCCC TTACGTCAAG GGAATCACTG GAAGGCCCAC TGCCCCAGGG 1380
GATGAAGATA CTCTGAGTCA GAAGCCATTA ACCAGATGAT CCAGCAGCAG GACTGAGGGT 1440
GCCCGGGGCG AGCGCCAGCC CATGCCATCA CCCTCACAGA GCCCCGGGTA TGTTTGACCA 1500
TTGAGAGCCA A                                                     1511
```

(2) INFORMATION FOR SEQ ID NO: 131:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 352 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 131:

```
Leu Glu Arg Ile Leu Glu Asn Trp Asp Gln Cys Asp Thr Gln Thr Leu
1               5                   10                  15
```

Arg Lys Lys Arg Phe Ile Phe Phe Cys Ser Thr Ala Trp Pro Gln Tyr
20 25 30
Pro Leu Gln Gly Arg Glu Thr Trp Leu Pro Glu Gly Ser Ile Asn Tyr
35 40 45
Asn Ile Ile Leu Gln Leu Asp Leu Phe Cys Arg Lys Glu Gly Lys Trp
50 55 60
Ser Glu Val Pro Tyr Val Gln Thr Phe Phe Ser Leu Arg Asp Asn Ser
65 70 75 80
Gln Leu Cys Lys Lys Cys Gly Leu Cys Pro Thr Gly Ser Pro Gln Ser
85 90 95
Pro Pro Pro Tyr Pro Ser Val Pro Ser Pro Thr Pro Ser Ser Thr Asn
100 105 110
Lys Asp Pro Pro Leu Thr Gln Thr Val Gln Lys Glu Ile Asp Lys Gly
115 120 125
Val Asn Asn Glu Pro Lys Ser Ala Asn Ile Pro Arg Leu Cys Pro Leu
130 135 140
Gln Ala Val Arg Gly Gly Glu Phe Gly Pro Ala Arg Val Pro Val Pro
145 150 155 160
Phe Ser Leu Ser Asp Leu Lys Gln Ile Lys Ile Asp Leu Gly Lys Phe
165 170 175
Ser Asp Asn Pro Asp Gly Tyr Ile Asp Val Leu Gln Gly Leu Gly Gln
180 185 190
Ser Phe Asp Leu Thr Trp Arg Asp Ile Met Leu Leu Leu Asn Gln Thr
195 200 205
Leu Thr Pro Asn Glu Arg Ser Ala Ala Val Thr Ala Ala Arg Glu Phe
210 215 220
Gly Asp Leu Trp Tyr Leu Ser Gln Ala Asn Asn Arg Met Thr Thr Glu
225 230 235 240
Glu Arg Thr Thr Pro Thr Gly Gln Gln Ala Val Pro Ser Val Asp Pro
245 250 255
His Trp Asp Thr Glu Ser Glu His Gly Asp Trp Cys His Lys His Leu
260 265 270
Leu Thr Cys Val Leu Glu Gly Leu Arg Lys Thr Arg Lys Lys Pro Met
275 280 285
Asn Tyr Ser Met Met Ser Thr Ile Thr Gln Gly Lys Glu Glu Asn Leu
290 295 300

Thr Ala Phe Leu Asp Arg Leu Arg Glu Ala Leu Arg Lys His Thr Ser
305 310 315 320
Leu Ser Pro Asp Ser Ile Glu Gly Gln Leu Ile Leu Lys Asp Lys Phe
325 330 335
Ile Thr Gln Ser Ala Ala Asp Ile Arg Lys Asn Phe Lys Ser Leu Pro
340 345 350

(2) INFORMATION FOR SEQ ID NO: 132:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 132:

TGCTGGAATT CGGGATCCTA GAACGTATTC 30

(2) INFORMATION FOR SEQ ID NO: 133:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 30 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 133:

AGTTCTGCTC CGAAGCTTAG GCAGACTTTT 30

(2) INFORMATION FOR SEQ ID NO: 135:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 398 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 135:

Met Gly Ser Ser His His His His His His Ser Ser Gly Leu Val Pro

```
1               5                   10                  15
Arg Gly Ser His Met Ala Ser Met Thr Gly Gly Gln Gln Met Gly Arg
            20                  25                  30
Ile Leu Glu Arg Ile Leu Glu Asn Trp Asp Gln Cys Asp Thr Gln Thr
        35                  40                  45
Leu Arg Lys Lys Arg Phe Ile Phe Phe Cys Ser Thr Ala Trp Pro Gln
    50                  55                  60
Tyr Pro Leu Gln Gly Arg Glu Thr Trp Leu Pro Glu Gly Ser Ile Asn
65                  70                  75                  80
Tyr Asn Ile Ile Leu Gln Leu Asp Leu Phe Cys Arg Lys Glu Gly Lys
                85                  90                  95
Trp Ser Glu Val Pro Tyr Val Gln Thr Phe Phe Ser Leu Arg Asp Asn
            100                 105                 110
Ser Gln Leu Cys Lys Lys Cys Gly Leu Cys Pro Thr Gly Ser Pro Gln
        115                 120                 125
Ser Pro Pro Pro Tyr Pro Ser Val Pro Ser Pro Thr Pro Ser Ser Thr
    130                 135                 140
Asn Lys Asp Pro Pro Leu Thr Gln Thr Val Gln Lys Glu Ile Asp Lys
145                 150                 155                 160
Gly Val Asn Asn Glu Pro Lys Ser Ala Asn Ile Pro Arg Leu Cys Pro
                165                 170                 175
Leu Gln Ala Val Arg Gly Gly Glu Phe Gly Pro Ala Arg Val Pro Val
            180                 185                 190
Pro Phe Ser Leu Ser Asp Leu Lys Gln Ile Lys Ile Asp Leu Gly Lys
        195                 200                 205
Phe Ser Asp Asn Pro Asp Gly Tyr Ile Asp Val Leu Gln Gly Leu Gly
    210                 215                 220
Gln Ser Phe Asp Leu Thr Trp Arg Asp Ile Met Leu Leu Leu Asn Gln
225                 230                 235                 240
Thr Leu Thr Pro Asn Glu Arg Ser Ala Ala Val Thr Ala Ala Arg Glu
                245                 250                 255
Phe Gly Asp Leu Trp Tyr Leu Ser Gln Ala Asn Asn Arg Met Thr Thr
            260                 265                 270
Glu Glu Arg Thr Thr Pro Thr Gly Gln Gln Ala Val Pro Ser Val Asp
        275                 280                 285
Pro His Trp Asp Thr Glu Ser Glu His Gly Asp Trp Cys His Lys His
```

290 295 300

Leu Leu Thr Cys Val Leu Glu Gly Leu Arg Lys Thr Arg Lys Lys Pro
305 310 315 320

Met Asn Tyr Ser Met Met Ser Thr Ile Thr Gln Gly Lys Glu Glu Asn
325 330 335

Leu Thr Ala Phe Leu Asp Arg Leu Arg Glu Ala Leu Arg Lys His Thr
340 345 350

Ser Leu Ser Pro Asp Ser Ile Glu Gly Gln Leu Ile Leu Lys Asp Lys
355 360 365

Phe Ile Thr Gln Ser Ala Ala Asp Ile Arg Lys Asn Phe Lys Ser Leu
370 375 380

Pro Lys Leu Ala Ala Ala Leu Glu His His His His His His
385 390 395

(2) INFORMATION FOR SEQ ID NO: 137:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 378 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 137:

Met Ala Ser Met Thr Gly Gly Gln Gln Met Gly Arg Ile Leu Glu Arg
1 5 10 15

Ile Leu Glu Asn Trp Asp Gln Cys Asp Thr Gln Thr Leu Arg Lys Lys
20 25 30

Arg Phe Ile Phe Phe Cys Ser Thr Ala Trp Pro Gln Tyr Pro Leu Gln
35 40 45

Gly Arg Glu Thr Trp Leu Pro Glu Gly Ser Ile Asn Tyr Asn Ile Ile
50 55 60

Leu Gln Leu Asp Leu Phe Cys Arg Lys Glu Gly Lys Trp Ser Glu Val
65 70 75 80

Pro Tyr Val Gln Thr Phe Phe Ser Leu Arg Asp Asn Ser Gln Leu Cys
85 90 95

Lys Lys Cys Gly Leu Cys Pro Thr Gly Ser Pro Gln Ser Pro Pro Pro
100 105 110

```
Tyr Pro Ser Val Pro Ser Pro Thr Pro Ser Ser Thr Asn Lys Asp Pro
        115                 120                 125
Pro Leu Thr Gln Thr Val Gln Lys Glu Ile Asp Lys Gly Val Asn Asn
    130                 135                 140
Glu Pro Lys Ser Ala Asn Ile Pro Arg Leu Cys Pro Leu Gln Ala Val
145                 150                 155                 160
Arg Gly Gly Glu Phe Gly Pro Ala Arg Val Pro Val Pro Phe Ser Leu
                165                 170                 175
Ser Asp Leu Lys Gln Ile Lys Ile Asp Leu Gly Lys Phe Ser Asp Asn
            180                 185                 190
Pro Asp Gly Tyr Ile Asp Val Leu Gln Gly Leu Gly Gln Ser Phe Asp
        195                 200                 205
Leu Thr Trp Arg Asp Ile Met Leu Leu Leu Asn Gln Thr Leu Thr Pro
    210                 215                 220
Asn Glu Arg Ser Ala Ala Val Thr Ala Ala Arg Glu Phe Gly Asp Leu
225                 230                 235                 240
Trp Tyr Leu Ser Gln Ala Asn Asn Arg Met Thr Thr Glu Glu Arg Thr
                245                 250                 255
Thr Pro Thr Gly Gln Gln Ala Val Pro Ser Val Asp Pro His Trp Asp
            260                 265                 270
Thr Glu Ser Glu His Gly Asp Trp Cys His Lys His Leu Leu Thr Cys
        275                 280                 285
Val Leu Glu Gly Leu Arg Lys Thr Arg Lys Lys Pro Met Asn Tyr Ser
    290                 295                 300
Met Met Ser Thr Ile Thr Gln Gly Lys Glu Glu Asn Leu Thr Ala Phe
305                 310                 315                 320
Leu Asp Arg Leu Arg Glu Ala Leu Arg Lys His Thr Ser Leu Ser Pro
                325                 330                 335
Asp Ser Ile Glu Gly Gln Leu Ile Leu Lys Asp Lys Phe Ile Thr Gln
            340                 345                 350
Ser Ala Ala Asp Ile Arg Lys Asn Phe Lys Ser Leu Pro Lys Leu Ala
        355                 360                 365
Ala Ala Leu Glu His His His His His His
    370                 375
```

(2) INFORMATION FOR SEQ ID NO: 138:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 138:

CTTGGAGGGT GCATAACCAG GGAAT 25

(2) INFORMATION FOR SEQ ID NO: 139:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 139:

TGTCCGCTGT GCTCCTGATC 20

(2) INFORMATION FOR SEQ ID NO: 140:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 140:

CTATGTCCTT TTGGACTGTT TGGGT 25

(2) INFORMATION FOR SEQ ID NO: 141:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 764 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 141:

```
TGTCCGCTGT GCTCCTGATC CAGCACAGGC GCCCATTGCC TCTCCCAATT GGGCTAAAGG   60
CTTGCCATTG TTCCTGCACA GCTAAGTGCC TGGGTTCATC CTAATCGAGC TGAACACTAG  120
TCACTGGGTT CCACGGTTCT CTTCCATGAC CCATGGCTTC TAATAGAGCT ATAACACTCA  180
CTGCATGGTC CAAGATTCCA TTCCTTGGAA TCCGTGAGAC CAAGAACCCC AGGTCAGAGA  240
ACACAAGGCT TGCCACCATG TTGGAAGCAG CCCACCACCA TTTTGGAAGC AGCCCGCCAC  300
TATCTTGGGA GCTCTGGGAG CAAGGACCCC AGGTAACAAT TTGGTGACCA CGAAGGGACC  360
TGAATCCGCA ACCATGAAGG GATCTCCAAA GCAATTGGAA ATGTTCCTCC CAAGGCAAAA  420
ATGCCCCTAA GATGTATTCT GGAGAATTGG GACCAATTTG ACCCTCAGAC AGTAAGAAAA  480
AAATGACTTA TATTCTTCTG CAGTACCGCC CTGGCCACGA TATCCTCTTC AAGGGGGAGA  540
AACCTGGCCT CCTGAGGGAA GTATAAATTA TAACACCATC TTACAGCTAG ACCTGTTTTG  600
TAGAAAAGGA GGCAAATGGA GTGAAGTGCC ATATTTACAA ACTTTCTTTT CATTAAAAGA  660
CAACTCGCAA TTATGTTAAC AGTGTGATTT GTGTTCCTAC ACGGAAGCCC TCAGATTCTA  720
CTCCCCACCC CCGGCATCTC CCCTGAATCC CTCCCCAACT TATT                   764
```

(2) INFORMATION FOR SEQ ID NO: 142:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 800 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 142:

```
TGTCCGCTGT GCTCCTGATC CAGCACAGGC GCCCATTGCC TCTCCCAATT GGGCTAAAGG   60
CTTGCCATTG TTCCTGCACA GCTAAGTGCC TGGGTTCATC CTAATCGAGC TGAACACTAG  120
TCACTGGGTT CCACGGTTCT CTTCCATGAC CCATGGCTTC TAATAGAGCT ATAACACTCA  180
CTGCATGGTC CAAGATTCCA TTCCTTGGAA TCCGTGAGAC CAAGAACCCC AGGTCAGAGA  240
ACACAAGGCT TGCCACCATG TTGGAAGCAG CCCACCACCA TTTTGGAAGC GGCCCGCCAC  300
TATCTTGGGA GCTCTGGGAG CAAGGACCCC CAGGTAACAA TTTGGTGACC ACGAAGGGAC  360
CTGAATCCGC AACCATGAAG GGATCTCCAA AGCAATTGGA AATGTTCCTC CCAAGGCAAA  420
AATGCCCCTA AGATGTATTC TGGAGAATTG GGACCAATCT GACCCTCAGA CAGTAAGAAA  480
AAAAATGACT TATATTCTTC TGCAGTACCG CCTGGCCACG GATATCCTCT TCAAGGGGGA  540
GAAACCTGGC CTCCTGAGGG AAGTATAAAT TATAACACCA TCTTACAGCT AGACCTGTTT  600
TGTAGAAAAG GAGGCAAATG GAGTGAAGTG CCATATTTAC AAACTTTCTT TTCATTAAAA  660
GACAACTCGC AATTATGTAA ACAGTGTGAT TTGTGTCCTA CAGGAAGCCC TCAGATCTAC  720
CTCCCTACCC CGGCATCTCC CTGACTCCTT CCCCAACTAA TAAGGACCCA CTTCAGCCCA  780
```

AACAGTCCAA AAGGACATAG 800

(2) INFORMATION FOR SEQ ID NO: 169:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:169:

consensus (41/68-1 + 42/68-1 + c143 68-1)

(2) INFORMATION FOR SEQ ID NO: 170:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 438 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:170:

GACTTGAGCC AGTCCTCATA CCTGGACACT CTTGTCCTTC GGTACATGGA TGATTTACTT 60
TTAGCCACCC ATTCAGAAAC CTTGTGCCAT CAAGCCACCC AAGCACTCTT AAATTTCCTT 120
GCTACCTGTG GCTACAAGGT TTCCAAACCA AAGGCTCAGC TCTGCTCACA GCAGGTTAAA 180
TACTTAGGGC TAAAATTATC CAAAGGCACC AGAACCCTCA GTGAGGAACG TATCCAGCCT 240
ATACTGGGTT ATCCTCATCC CAAAACCCTA AAGCAACTAA CAGCGTTCCT TGGCATAACA 300
GGTTTCTGCC AAATATGGAT TCCCAGGTAC AGCAAGATAG CCAGACCATT AAATACACGA 360
ATTAAGGAAA CTCAAAAAGC CAATACCCAT TTAGTAAGAT GGACACCTGA AGCAGAAGTG 420
GCTTTCCAGG CCCTAAAG 438

(2) INFORMATION FOR SEQ ID NO: 171:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 438 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:171:

GACTTGAGCC AGTCCTCATA CCTGGACACT CTTGTCCTTC GGTACATGGA TGATTTACTT 60
TTAGCCACCC ATTCAGAAAC CTTGTGCCAT CAAGCCACCC AAGCACTCTT AAATTTCCTT 120
GCTACCTGTG GCTACAAGGT TTCCAAACCA AAGGCTCAGC TCTGCTCACA GCAGGTTAAA 180
TACTTAGGGC TAAAATTATC CAAAGGCACC AGAACCCTCA GTGAGGAACG TATCCAGCCT 240
ATACTGGGTT ATCCTCATCC CAAAACCCTA AAGCAACTAA CAGCGTTCCT TGGCATAACA 300
GGTTTCTGCC AAATATGGAT TCCCAGGTAC AGCAAAGTAG CCAGACCATT AAATACACGA 360
ATTAAGGAAA CTCAAAAAGC CAGTACCCAT TTAGTAAGAT GGACACCTGA AGCAGAAGTG 400
GCTTTCCAGG CCCTAAAG 438

(2) INFORMATION FOR SEQ ID NO: 172:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 438 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:172:

GACTTGAGCC AGTCYTCATA CCTGGACAYT CTTGTCCTTC GGTACATGGA TGATTTACTT 60
TTAGCCACCC ATTCAGAAAC CTTGTGCCAT CAAGCCACCC AAGCACTCTT AAATTTCCTT 120
GCTACCTGTG GCTACAAGGT TTCCAAACCA AAGGCTCAGC TCTGCTCACA GCAGGTTAAA 180
TACTTAGGGC TAAAATTATC CAAAGGCACC AGAACCCTCA GTGAGGAACG TATCCAGCCT 240
ATACTGGGTT ATCCTCATCC CAAAACCCTA AAGCAACTAA CAGCGTTCCT TGGCATAACA 300
GGTTTCTGCC AAATATGGAT TCCCAGGTAC AGCAAAATAG CCAGACCATT AAATACACGA 360
ATTAAGGAAA CTCAAAAAGC CAATACCCAT TTAGTAAGAT GGACATCTGA AGCAGAAGTG 400
GCTTTCCAGG CCCTAAAG 438

(2) INFORMATION FOR SEQ ID NO: 173:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 146 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:173:

DLSQSSYLDT LVLRYMDDLL LATHSETLCH QATQALLNFL ATCGYKVSKP 50

KAQLCSQQVK YLGLKLSKGT RTLSEERIQP ILGYPHPKTL KQLTAFLGIT 100

GFCQIWIPRY SKIARPLNTR IKETQKANTH LVRWTPEAEV AFQALK 146

(2) INFORMATION FOR SEQ ID NO: 174:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 146 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:174:

DLSQSSYLDT LVLRYMDDLL LATHSETLCH QATQALLNFL ATCGYKVSKP 50

KAQLCSQQVK YLGLKLSKGT RTLSEERIQP ILGYPHPKTL KQLTAFLGIT 100

GFCQIWIPRY SKVARPLNTR IKETQKASTH LVRWTPEAEV AFQALK 146

(2) INFORMATION FOR SEQ ID NO: 175:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 146 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:175:

DLSQSSYLDX LVLRYMDDLL LATHSETLCH QATQALLNFL ATCGYKVSKP 50

KAQLCSQQVK YLGLKLSKGT RTLSEERIQP ILGYPHPKTL KQLTAFLGIT 100

GFCQIWIPRY SKIARPLNTR IKETQKANTH LVRWTSEAEV AFQALK 146

(2) INFORMATION FOR SEQ ID NO: 176:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:176:

consensus (1/46-7+8/46-7+c15/46/7)

(2) INFORMATION FOR SEQ ID NO: 177:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 429 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:177:

```
GACTTGAGCC AGTCCTCATA CCTGGACATT CTTGTTCTTC AGTATGGGGA TGACTTAATT    60
ATAGCCACCC ATTCAGAAAC CTTGTGGCAT CAAGCCACCC AAGCGCTCTT AAATTTCCTT   120
GCTACCTGTG GCTCCAAACA AAAGGCTCAC CTCTGCTCAC ACCAGGTTAA ATACTTAGGG   180
CTAAAATTAT CCAAAGTCAC CAGGGCCCTC AGAGAGGAAC GTATCCAGCG TATACTGGCT   240
TATCCTCATC CCATAACCCT AAAGCAACTA AGAGGGTTCC TTGGCATATC AGCCTTCTGC   300
CGAATATGGA TTCCCGGATA CAGTGAAATA GCCAGGCCAT TATGTACATT AATTAAGGAA   360
ACTCAGAAAG CCAATACCCA TATAGTAAGA TGGACACCTG AAACAGAAGT GGCTTTCCAG   420
GCCCTAAAG                                                           429
```

(2) INFORMATION FOR SEQ ID NO: 178:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 429 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:178:

```
GACTTGAGCC AGTCCTCATA CCTGGACATT CTTGTTCTTC AGTATAGGGA TGATTTAATT    60
ATAGCCACCC ATTCAGAAAC CTTGTGGCAT CAAGCCACCC AAGTGCTCTT AAATTTCCTC   120
GCTACCTGTG GCTCCAAACA AAGGGCTCAG CTCTGCTCAC AGCAGGTTAA ATACTTAGGG   180
CTAAAATTAT CCAAAGTCGC CAGGGCCCTC AGAGAGGAAC GTATCCAGCG TATACTGGAT   240
TATCCTCATC CCAAAACCAT AAAGCAACTA AGAGGGTTCC TTGGCATAAC AGCCTTCTGC   300
CGAATATGGA TTCCCCGATA CAGTGAAATA GCCAGGCCAT TATGTACATT AGTTAAGGAA   360
ACTCAGAAAG CCAATACCCA TATAGTAAGA TGGACACCTG AGACAGAAGT GGCTTTCCAG   420
GCCCTAAAG                                                           429
```

(2) INFORMATION FOR SEQ ID NO: 179:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 429 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:179:

```
GACTTGAGCC AGTCCTCATA CCTGGACATT CTTGTTCCTC AGTATGGGGA TGATTTAATT   60
ATAGCCACCC ATTCAGAAAC CTTGTGGCAC CAAGCCACCC AAGCGCTCTT AAATTTCCTC  120
GCTACCTGTG GCTCCAAACA AAAGGCTCAG CTCTGCTCAC AGCAGGTTAA ATACTTAGGG  180
CTAAAATTAT CCAAAGTCAC CAGGGCCCTC AGAGAGGAAC GTATCCAGCG TATACTGGCT  240
TATCCCCATC CCAAAACCCT AAAGCAACTA AGARGGTTCC TTGGCATAAC AGCCTTCTGC  300
CGAATATGGA TTCCCAGATA CAGCGAAATA GCCAGGCCAT TATGTACATT ATCTAAGGAA  360
ACTCAGAAAG CCAATACCCA TATAGTAAGA TGGACACCTG AAACAGAAGT GGCTTTCCAG  420
GCCCTAAAG                                                          429
```

(2) INFORMATION FOR SEQ ID NO: 180:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 143 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:180:

```
DLSQSSYLDI LVLQYGDDLI IATHSETLWH QATQALLNFL ATCGSKQKAH    50
LCSHQVKYLG LKLSKVTRAL REERIQRILA YPHPITLKQL RGFLGISAFC   100
RIWIPGYSEI ARPLCTLIKE TQKANTHIVR WTPETEVAFQ ALK          143
```

(2) INFORMATION FOR SEQ ID NO: 181:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 143 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:181:

DLSQSSYLDI LVLQYRDDLI IATHSETLWH QATQVLLNFL ATCGSKQRAQ 50
LCSQQVKYLG LKLSKVARAL REERIQRILD YPHPKTIKQL RGFLGITAFC 100
RIWIPRYSEI ARPLCTLVKE TQKANTHIVR WTPETEVAFQ ALK 143

(2) INFORMATION FOR SEQ ID NO: 182:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 143 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) TYPE DE MOLECULE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:182:
DLSQSSYLDI LVPQYGDDLI IATHSETLWH QATQALLNFL ATCGSKQKAQ 50
LCSQQVKYLG LKLSKVTRAL REERIQRILA YPHPKTLKQL RXFLGITAFC 100
RIWIPRYSEI ARPLCTLSKE TQKANTHIVR WTPETEVAFQ ALK 143

(2) INFORMATION FOR SEQ ID NO: 183:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) TYPE DE MOLECULE: ADNc
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:183:
GGCCAGGCAT CAGCCCAAGA CTTGA 25

(2) INFORMATION FOR SEQ ID NO: 184:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 22 base pairs
(B) TYPE: nucleotide
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) TYPE DE MOLECULE: ADNc
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:184:
TGCAAGCTCA TCCCTSRGAC CT 22

(2) INFORMATION FOR SEQ ID NO: 185:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:185:

GACTTGAGCC AGTCCTCATA CCT 23

(2) INFORMATION FOR SEQ ID NO: 186:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleotide

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) TYPE DE MOLECULE: ADNc

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:186:

CTTTAGGGCC TGGAAAGCCA CT 22

TABLE No. 5

SEQUENCES GENERATED BY 'PAN-RETROVIRUS' PCR OF DENSITY GRADIENT FRACTIONS

(containing the peak of RT-activity or the corresponding control fraction)

CULTURE	MSRV c-pol	ERV9 (v)	PCR artefacts (vi)	Total clones
LM7P (I)	16	4	6	26
PLI-1 (II)	9	1	13	23
MS B-CELL LINE (III)	9	2	8	19
CONTROL B-CELL LINE (iv)	0	0	26	26

- I LM7-infected choroid plexus cell culture .
- II MS patient-derived choroid plexus cell culture (PLI-2).
- III MS patient-derived spontaneous B-cell line (immortalized by endogenous EBV strain).
- iv Non-MS control B-cell line.
- v Clones with >90% homology with the GenBank sequence HSERV9 are designated ERV9 in this study.
- vi PCR artefacts included primer multimers, concatemers, single primer amplifications, etc.

TABLE No. 6

DETECTION OF HMSRV IN THE CSF OF PATIENTS WITH MULTIPLE SCLEROSIS AND OTHER NEUROLOGICAL DISEASES

Patient[1]	Age/Sex	Diagnosis	MS Type	MS Activity	MS Duration	MS Treatment at sampling	MSRV ELOSA
ITMS1	27 yrs / M	multiple sclerosis	2° progressive	slow progression	5 yrs	corticosteroids	negative
ITMS2	55 yrs / M	multiple sclerosis	1° progressive	slow progression	9 yrs	none	POSITIVE
ITMS3	51 yrs / F	multiple sclerosis	1° progressive	slow progression	2 yrs	none	negative
ITMS4	22 yrs / F	multiple sclerosis	relapsing /remitting	in remission	0 yrs	none	POSITIVE
ITMS5	27 yrs / F	multiple sclerosis	1° progressive	slow progression	6 yrs	cyclophosphamide	negative
ITMS6	33 yrs / M	multiple sclerosis	2° progressive	slow progression	16 yrs	none (previously cycloph.+corticost.)	negative
ITMS7	33 yrs / F	multiple sclerosis	2° progressive	slow progression	9 yrs	none	POSITIVE
ITMS8	25 yrs / F	multiple sclerosis	relapsing /remitting	stable	3 yrs	none	POSITIVE
ITMS9	38 yrs / F	multiple sclerosis	2° progressive	slow progression	3 yrs	none	POSITIVE
ITMS10	38 yrs / M	multiple sclerosis	2° progressive	slow progression	7 yrs	corticosteroids	negative
OND1	37 yrs / F	cerebellar atrophy	NA[2]	NA	NA	NA	negative
OND2	26 yrs / F	viral myelitis	NA	NA	NA	NA	negative
OND3	38 yrs / F	viral encephalitis	NA	NA	NA	NA	negative
OND4	28 yrs / F	viral encephalitis	NA	NA	NA	NA	negative
OND5	64 yrs / M	viral encephalitis	NA	NA	NA	NA	negative
OND6	32 yrs / M	Guillain - Barré	NA	NA	NA	NA	negative
OND7	54 yrs / F	cerebrovascular	NA	NA	NA	NA	negative
OND8	52 yrs / F	hydrocephalus	NA	NA	NA	NA	negative
OND9	25 yrs / F	1° cerebral tumour	NA	NA	NA	NA	negative
OND10	21 yrs / M	epilepsy	NA	NA	NA	NA	negative

[1] CSF samples from patients ITMS1 - OND2 were made available by Prof. P. Ferranto, University Centre for Multiple Sclerosis, Milan, Italy.
CSF samples from patients OND3 - OND10 were made available by Profs. J. Pellat and J. Perret, Dept. of Neurology, University Hospital, Grenoble, France.

[2] NA = Not Applicable

CLAIMS

1. Nucleic material, in the isolated or purified state, comprising a nucleotide sequence selected from the group including sequences SEQ ID NO:93, SEQ ID NO:94, their complementary sequences and their equivalent sequences, in particular nucleotide sequences displaying, for any succession of 100 contiguous monomers, at least 50% and preferably at least 60% homology with said sequence SEQ ID NO:93, SEQ ID NO:94 and their complementary sequences, excluding HSERV-9 sequence.

2. Nucleic material of claim 1, nucleotide sequence of which is selected from the group including sequences SEQ ID NO:93, SEQ ID NO:94, their complementary sequences and their equivalent sequences, in particular nucleotide sequences displaying, for any succession of 100 contiguous monomers, at least 70% and preferably at least 80% homology with said sequence SEQ ID NO:93, SEQ ID NO:94 and their complementary sequences.

3. Nucleic material, in the isolated or purified state, coding for any polypeptide displaying, for any contiguous succession of at least 30 amino acids, at least 50%, preferably at least 60 %, and most preferably at least 70% homology with a peptide sequence encoded by any nucleotide sequence selected from the group including SEQ ID NO:93, SEQ ID NO:94 and their complementary sequence.

4. Nucleic material, in the isolated or purified state, of retroviral type, comprising a nucleotide sequence identical or equivalent to at least part of the pol gene of an isolated retrovirus associated with multiple sclerosis or rheumatoid arthritis.

5. Nucleic material as claimed in claim 4, said nucleotide sequence being 80 % homologous to said at least part of the pol gene.

6. Nucleic material comprising a nucleotide sequence identical or equivalent to at least part of the pol gene of an isolated virus encoding a reverse transcriptase comprising an enzymatic site comprised between the amino acid domains LPQG and YXDD, said virus having a phylogenic distance with HSERV-9 of 0.063 $\pm$ 0.1, and preferably 0.063 $\pm$ 0.05.

7. Nucleotide fragment comprising a nucleotide sequence selected from the group including SEQ ID NO:93, SEQ ID NO: 94, their complementary sequences and their equivalent sequences, in particular nucleotide sequences displaying, for any succession of 100 contiguous monomers, at least 50% and preferably at least 60% homology with said sequences and their complementary sequences, said group excluding SEQ ID NO:1, and said nucleotide fragment not comprising nor consisting of the sequence HSERV-9.

8. Nucleotide fragment of claim 7, nucleotide sequence of which is selected from the group including SEQ ID NO:93, SEQ ID NO: 94, their complementary sequences and their equivalent sequences, in particular nucleotide sequences displaying, for any succession of 100 contiguous monomers, at least 70% and preferably at least 80% homology with said sequences and their complementary sequences.

9. Nucleotide fragment comprising a coding nucleotide sequence which is at least partially identical to a nucleotide sequence selected from the group including :

SEQ ID NO:93, SEQ ID NO:94; their complementary sequences ; their equivalent sequences, in particular homologous to SEQ ID NO:93, SEQ ID NO:94;

sequences encoding at least part of the peptide sequence defined by SEQ ID NO:95;

sequences encoding at least part of a peptide sequence equivalent, in particular homologous to SEQ ID NO:95, which is capable of being recognized by sera of

patients infected with the MSRV-1 virus, or in whom the MSRV-1 virus has been reactivated.

10. Nucleic acid probe for the detection of a virus associated with multiple sclerosis or rheumatoid arthritis, characterized in that it is capable of hybridizing specifically with any fragment according to any one of claim 7 to 9.

11. Probe as claimed in claim 10, consisting of between 10 and 1,000 monomers.

12. Primer for the amplification by polymerization of an RNA or a DNA of a viral material associated with multiple sclerosis or rheumatoid arthritis, comprising a nucleotide sequence identical or equivalent to at least one portion of the nucleotide sequence of a fragment as claimed in any one of claims 7 to 9, in particular a nucleotide sequence displaying, for any succession of at least 10 contiguous monomers, preferably 15 contiguous monomers, more preferably 18 contiguous monomers and even most preferably 20 contiguous monomers, at least 70% homology with at least the said portion of the said fragment.

13. Primer as claimed in Claim 12, comprising a sequence selected from the group consisting of SEQ ID NO: 99 to SEQ ID NO: 111.

14. Polypeptide encoded by any open reading frame belonging to a nucleotide fragment as claimed in any one of claims 7 to 9.

15. Polypeptide of claim 14, characterized in that the open reading frame encoding it, is comprised, in the 5'-3' direction, between nucleotide 18 and nucleotide 2304 of SEQ ID NO:93.

16. Polypeptide according to claim 15, comprising a peptide sequence at least partially identical to SEQ ID NO: 95.

17. Polypeptide, comprising a peptide sequence at least partially identical to SEQ ID NO: 96.

18. Polypeptide of claim 17 exhibiting an enzymatic activity consisting of proteolytic activity.

19. Polypeptide, characterized in that the open reading frame encoding it begins, in the 5'-3' direction, at nucleotide 18 and ends at nucleotide 340 of SEQ ID NO:93.

20. Polypeptide exhibiting an inhibitory activity on the proteolytic activity of polypeptide of claim 18.

21. Polypeptide, comprising a peptide sequence identical or equivalent to SEQ ID NO: 97.

22. Polypeptide of claim 21, comprising a peptide sequence identical or equivalent to SEQ ID NO: 98.

23. Polypeptide, characterized in that the open reading frame encoding it begins, in the 5'-3' direction, at nucleotide 341 and ends at nucleotide 2304 of SEQ ID NO:93.

24. Polypeptide, characterized in that the open reading frame encoding it begins, in the 5'-3' direction, at nucleotide 1858 and ends at nucleotide 2304 of SEQ ID NO:93.

25. Polypeptide of claim 21 or 23, exhibiting a reverse transcriptase activity.

26. Polypeptide of claim 22 or 24, exhibiting a ribonuclease H activity.

27. Polypeptide exhibiting an inhibitory activity on the reverse transcriptase activity of polypeptide of claim 25.

28. Polypeptide having an inhibitory activity on the ribonuclease H activity of polypeptide of claim 26.

29. Antigenic polypeptide recognized from the sera of patients infected with the MSRV-1 virus, and/or in whom the MSRV-1 virus has been reactivated, characterized in that its peptide sequence is at least partially identical or is equivalent to a sequence selected from the group consisting of SEQ ID NO:95, and fragments thereof,

in particular SEQ ID NO:96, SEQ ID NO:97 and SEQ ID NO: 98.

30. Mono- or polyclonal antibody directed against the MSRV-1 virus, characterized in that it is obtained by the immunological reaction of a human or animal body or cells to an immunogenic agent consisting of an antigenic polypeptide of claim 29.

31. Reagent for detection of the MSRV-1 virus, or of an exposure to the said virus, characterized in that it comprises at least one reactive substance selected from the group consisting of a probe as claimed in claim 10 or 11 ; a polypeptide as claimed in any one of claims 14 to 29 ; or an antibody as claimed in claim 30.

32. Diagnostic, prophylactic or therapeutic composition, in particular for inhibiting the expression of a virus associated with multiple sclerosis or rheumatoid arthritis, and/or the enzymatic activity of the proteins of said virus, said composition comprising a nucleotide fragment of any one of claims 7 to 9.

33. Diagnostic, prophylactic or therapeutic composition comprising a polypeptide of any one of claims 14 to 29, or an antibody of claim 30.

34. Process for detecting a virus associated with multiple sclerosis or rheumatoid arthritis, in a biological sample, characterized in that an RNA and/or a DNA presumed to belong or originating from said virus, or their complementary RNA and/or DNA, is/are brought into contact with a nucleotide fragment according to any one of claim 7 to 9.

35. Process for detecting the presence or exposure to a virus associated with multiple sclerosis or rheumatoid arthritis, in a biological sample, wherein said sample is brought into contact with a polyeptide, according to any one of claim 14 to 29, or an antibody of claim 30.

FIG. 1

Consensus GTTTAGGGAT ANCCCTCATC TCTTTGGTCA GGTACTGGCC CAAGATCTAG 50
Consensus GCCACTTCTC AGGTCCAGSN ACTCTGTYCC TTCAG 85

SEQ ID NO3 (POL MSRV-1B)

Consensus GTTCAGGGAT AGCCCCCATC TATTTGGCCA GGCACTAGCT CAATACTTGA 50
Consensus GCCAGTTCTC ATACCTGGAC AYTCTYGTCC TTGGGT 86

SEQ ID NO4 (POL MSRV-1B)

Consensus GTTCARRGAT AGCCCCCATC TATTTGGCCW RGYATTAGCC CAAGACTTGA 50
Consensus GYCAATTCTC ATACCTGGAC ACTCTTGTCC TTYRG 85

SEQ ID NO5 (POL MSRV-1B)

Consensus GTTCAGGGAT AGCTCCCATC TATTTGGCCT GGCATTAACC CGAGACTTAA 50
Consensus GCCAGTTCTY ATACGTGGAC ACTCTTGTCC TTTGG 85

SEQ ID NO6 (POL MSRV-1B)

Consensus GTGTTGCCAC AGGGGTTTAR RGATANCYCY CATCTMTTTG GYCWRGYAYT
Consensus RRCYCRAKAY YTRRGYCAVT TCTYAKRYSY RGSNAYTCTB KYCCTTYRGT
Consensus ACATGGATGA C

SEQ ID NO7 (POL MSRV-1B)

FIG. 2

CONSENSUS A SEQ ID NO 3

GTTTAGGGATAGCCC TCATCTCTTGGTCA GGTACTGGCCCAAGA TCTAGGCCACTTCTC 60
V . G . P S S L W S G T G P R S R P L L
F R D S P H L F G Q V L A Q D L G H F S
L G I A L I S L V R Y W P K I . A T S Q

AGGTCCAGGCACTCT GTTCCTTCAG 85
R S R H S V P S
G P G T L F L Q
V Q A L C S F

CONSENSUS B SEQ ID NO 4

GTTCAGGGATAGCCC CCATCTATTTGGCCA GGCACTAGCTCAATA CTTGAGCCAGTTCTC 60
V Q G . P P S I W P G T S S I L E P V L
F R D S P H L F G Q A L A Q Y L S Q F S
S G I A P I Y L A R H . L N T . A S S H

ATACCTGGACACTCT TGTCCTTCGGT 86
I P G H S C P S
Y L D T L V L R
T W T L L S F G

CONSENSUS C SEQ ID NO 5

GTTCAGGGATAGCCC CCATCTATTTGGCCA GGCATTAGCCCAAGA CTTGAGTCAATTCTC 60
V Q G . P P S I W P G I S P R L E S I L
F R D S P H L F G Q A L A Q D L S Q F S
S G I A P I Y L A R H . P K T . V N S H

ATACCTGGACACTCT TGTCCTTCAG 85
I P G H S C P S
Y L D T L V L Q
T W T L L S F

CONSENSUS D SEQ ID NO 6

GTTCAGGGATAGCTC CCATCTATTTGGCCT GGCATTAACCCGAGA CTTAAGCCAGTTCTC 60
V Q G . L P S I W P G I N P R L K P V L
F R D S S H L F G L A L T R D L S Q F S
S G I A P I Y L A W H . P E T . A S S H

ATACGTGGACACTCT TGTCCTTTGG 85
I R G H S C P L
Y V D T L V L W
T W T L L S F

FIG. 3

Consensus	TTGGATCCAG TGYTGCCACA GGGCGCTGAA GCCTATCGCG TGCAGTTGCC	50
Consensus	GGATGCCGCC TATAGCCTCT ACGTGGATGA CCTSCTGAAG CTTGAG	96

SEQ ID NO 11

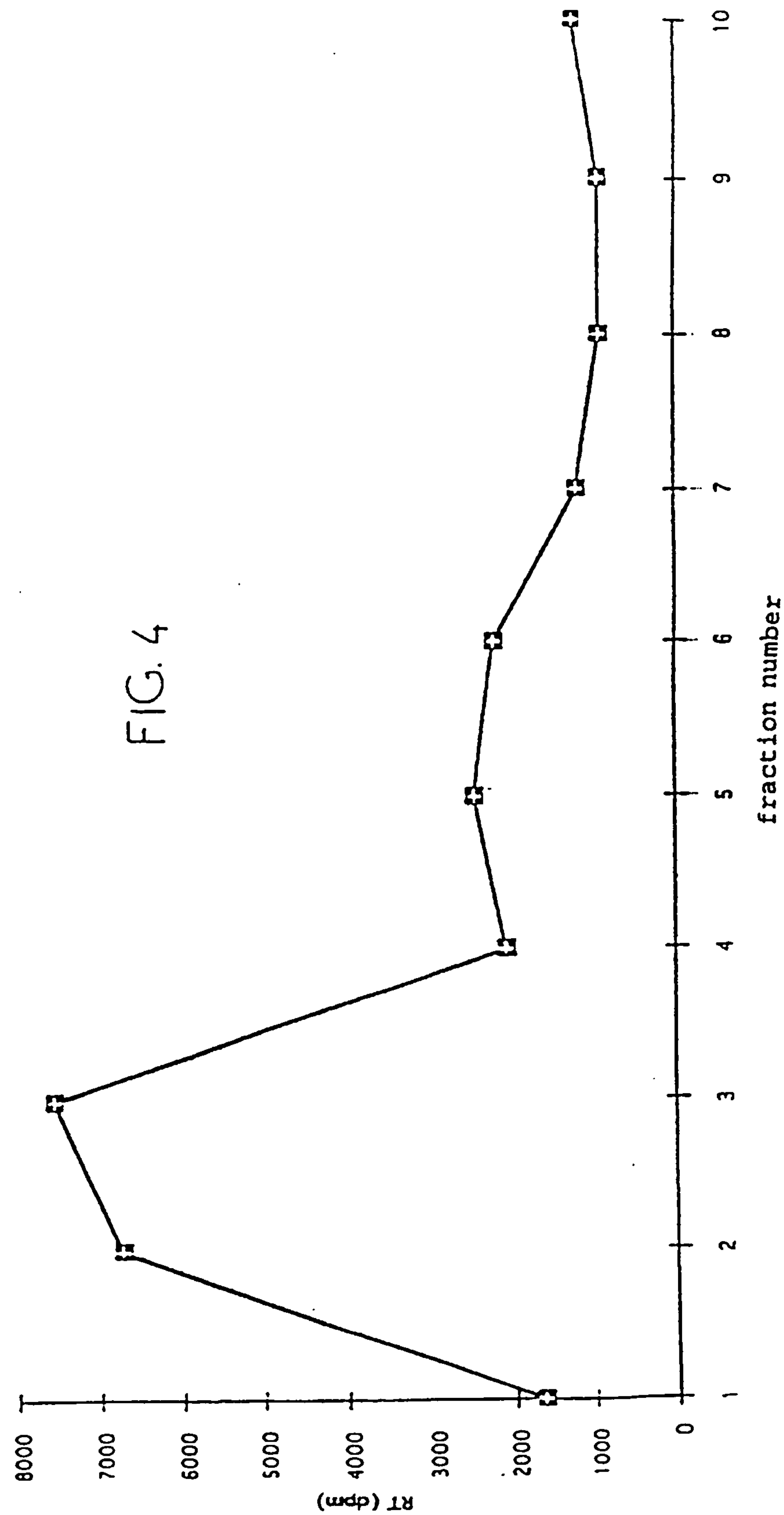

RT (dpm)
0
1000
2000
3000
4000
5000
6000
7000
8000
1
2
3
4
5
6
7
8
9
10
fraction number

FIG. 4

5/69

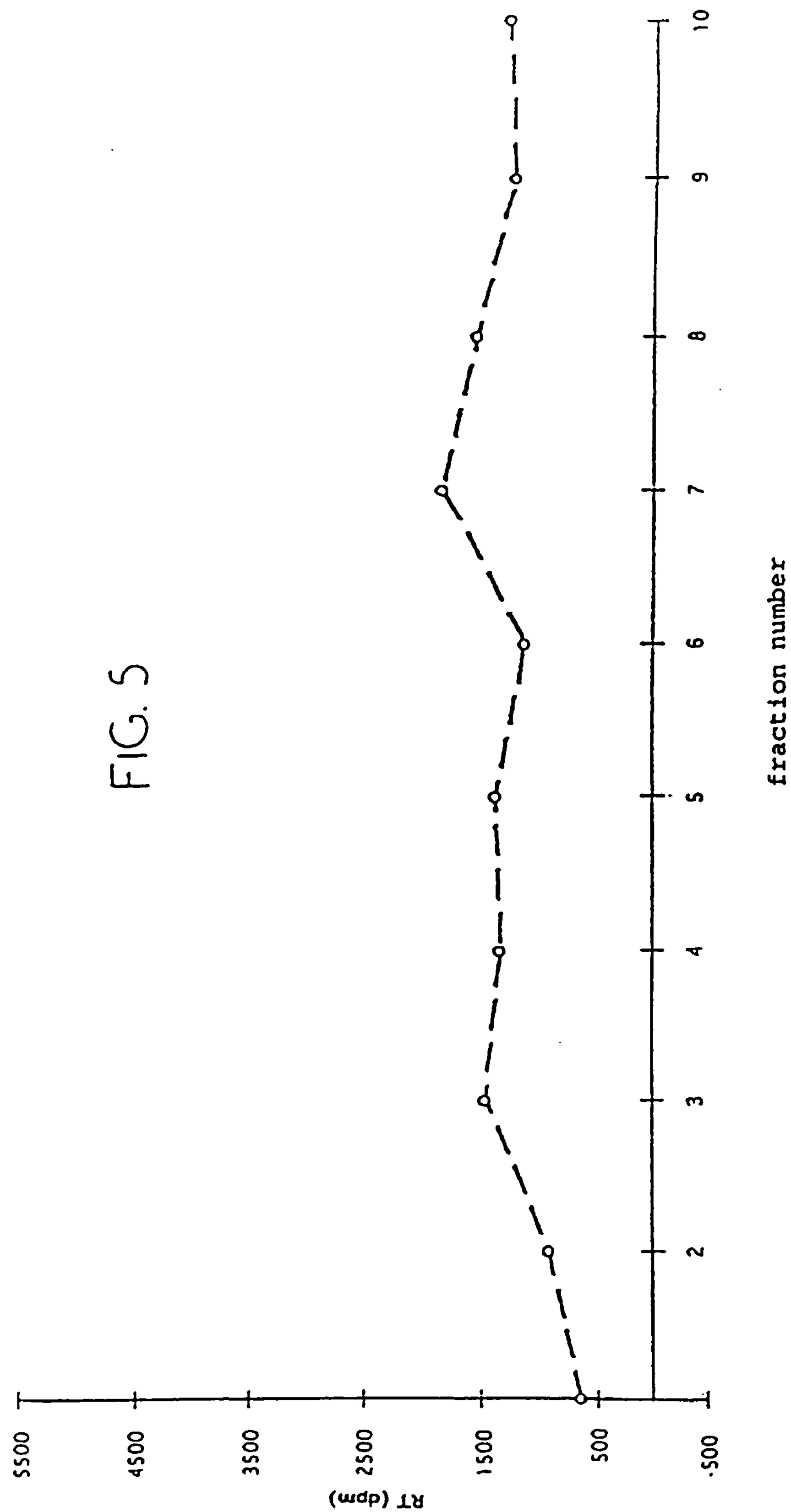

RT (dpm)
5500
4500
3500
2500
1500
500
-500
fraction number
2
3
4
5
6
7
8
9
10

FIG. 5

FIG. 6

CAAGCCACCC AAGAACTCTT AAATTTCCTC ACTACCTGTG GCTACAAGGT 50
TTCCAAACCA AAGGCTCAGC TCTGCTCACA GGAGATTAGA TACTTAGGGT 100
TAAAATTATC CAAAGGCACC AGGGGCCTCA GTGAGGAACG TATCCAGCCT 150
ATACTGGGTT ATCCTCATCC CAAAACCCTA AAGCAACTAA GAGGGTTCCT 200
TAGCATGATC AGGTTTCTGC CGAAAACAAG ATTCCCAGGT ACAACCAAAA 250
TAGCCAGACC ATTATATACA CTAATTAAGG AAACTCAGAA AGCCAATACC 300
TATTTAGTAA GATGGACACC TAAACAGAAG GCTTTCCAGG CCCTAAAGAA 350
GGCCCTAACC CAAGCCCCAG TGTTCAGCTT GCCAACAGGG CAAGATTTTT 400
CTTTATATGG CACAGAAAAA ACAGGAATCG CTCTAGGAGT CCTTACACAG 450
GTCCGAGGGA TGAGCTTGCA ACCCGTGGCA TACCTGAATA AGGAAATTGA 500
TGTAGTGGCA AAGGGTTGGC CTCATNGTTT ATGGGTAATG GNGGCAGTAG 550
CAGTCTNAGT ATCTGAAGCA GTTAAAATAA TACAGGGAAG AGATCTTNCT 600
GTGTGGACAT CTCATGATGT GAACGGCATA CTCACTGCTA AAGGAGACTT 650
GTGGTTGTCA GACAACCATT TACTTAANTA TCAGGCTCTA TTACTTGAAG 700
AGCCAGTGCT GNGACTGCGC ACTTGTGCAA CTCTTAAACC C 741

SEQ ID NO9 (PSJ 17)

TCAGGGATAGCCCCCATCTATTTGGCCAGGCATTAGCCCAAGACTTGAGTC
AATTCTCATACCTGGACACTCTTGTCCTTCAGTACATGGATGATTTACTTT
TAGTCGCCCGTTCAGAAACCTTGTGCCATCAAGCCACCCAAGAACTCTTAA
CTTTCCTCACTACCTGTGGCTACAAGGTTTCCAAACCAAAGGCTCGGCTCT
GCTCACAGGAGATTAGATACTNAGGGCTAAAATTATCCAAAGGCACCAGG
GCCCTCAGTGAGGAACGTATCCAGCCTATACTGGCTTATCCTCATCCCAAA
ACCCTAAAGCAACTAAGAGGGTTCCTTGGCATAACAGGTTTCTGCCGAAA
ACAGATTCCCAGGTACASCCCAATAGCCAGACCATTATATACACTAATTA
NGGAAACTCAGAAAGCCAATACCTATTTAGTAAGATGGACACCTACAGAA
GTGGCTTTCCAGGCCCTAAAGAAGGCCCTAACCCAAGCCCCAGTGTTCAGC
TTGCCAACAGGGCAAGATTTTTCTTTATATGCCACAGAAAAAACAGGAAT
AGCTCTAGGAGTCCTTACGCAGGTCTCAGGGATGAGCTTGCAACCCGTGGT
ATACCTGAGTAAGGAAATTGATGTAGTGGCAAAGGGTT

SEQ ID NO 8 (MOO3-POO4)

FIG. 7

SEQ ID NO 2 (F11-1)

```
                 10                  20                  30                  40                  50                  60                  70
                  *                   *                   *                   *                   *                   *                   *
CCC TTT GCC ACT ACA TCA ATT TTA GGA GTA AGG AAA CCC AAC GGA CAG TGG AGG TTA GTG CAA GAA CTC AGG
 P   F   A   T   T   S   I   L   G   V   R   K   P   N   G   Q   W   R   L   V   Q   E   L   R>
___a___a___a___a___a___a___a___a___TRANSLATION OF F11-1 [A]____a___a___a___a___a___a___a___a___>

             80                  90                 100                 110                 120                 130                 140
              *                   *                   *                   *                   *                   *                   *
ATT ATC AAT GAG GCT GTT GTT CCT CTA TAC CCA GCT GTA CCT AAC CCT TAT ACA GTG CTT TCC CAA ATA CCA
 I   I   N   E   A   V   V   P   L   Y   P   A   V   P   N   P   Y   T   V   L   S   Q   I   P>
___a___a___a___a___a___a___a___a___TRANSLATION OF F11-1 [A]____a___a___a___a___a___a___a___a___>

     150                 160                 170                 180                 190                 200                 210
      *                   *                   *                   *                   *                   *                   *
GAG GAA GCA GAG TGG TTT ACA GTC CTG GAC CTT AAG GAT GCC TTT TTC TGC ATC CCT GTA CGT CCT GAC TCT
 E   E   A   E   W   F   T   V   L   D   L   K   D   A   F   F   C   I   P   V   R   P   D   S>
___a___a___a___a___a___a___a___a___TRANSLATION OF F11-1 [A]____a___a___a___a___a___a___a___a___>

   220                 230                 240                 250                 260                 270                 280
    *                   *                   *                   *                   *                   *                   *
CAA TTC TTG TTT GCC TTT GAA GAT CCT TTG AAC CCA ACG TCT CAA CTC ACC TGG ACT GTT TTA CCC CAA GGG
 Q   F   L   F   A   F   E   D   P   L   N   P   T   S   Q   L   T   W   T   V   L   P   Q   G>
___a___a___a___a___a___a___a___a___TRANSLATION OF F11-1 [A]____a___a___a___a___a___a___a___a___>

290
 *
TTC AAG GGA
 F   K   G>
___a___a___>
```

FIG. 8

```
        10         20         30         40         50         60         70
CCC TTT GCC ACT ACA TCA ATT TTA GGA GTA AGG AA. CCC AAC GGA CAG TGG AGG TTA GTG CAA GAA CTC AGG
 P   F   A   T   T   S   I   L   G   V   R   K   P   N   G   Q   W   R   L   V   Q   E   L   R>
TRANSLATION OF MSRV-1 POL * (A)

        80         90        100        110        120        130        140
ATT ATC AAT GAG GCT GTT GTT CCT CTA TAC CCA GCT GTA CCT AAC CCT TAT ACA GTG CTT TCC CAA ATA CCA
 I   I   N   E   A   V   V   P   L   Y   P   A   V   P   N   P   Y   T   V   L   S   Q   I   P>
TRANSLATION OF MSRV-1 POL * (A)

    150        160        170    A  180        190        200        210
GAG GAA GCA GAG TGG TTT ACA GTC CTG GAC CTT AAG GAT GCC TTT TTC TGC ATC CCT GTA CGT CCT GAC TCT
 E   E   A   E   W   F   T   V   L   D   L   K   D   A   F   F   C   I   P   V   R   P   D   S>
TRANSLATION OF MSRV-1 POL * (A)

    220        230        240        250        260        270        280
CAA TTC TTG TTT GCC TTT GAA GAT CCT TTG AAC CCA ACG TCT CAA CTC ACC TGG ACT GTT TTA CCC CAA GGG
 Q   F   L   F   A   F   E   D   P   L   N   P   T   S   Q   L   T   W   T   V   L   P   Q   G>
TRANSLATION OF MSRV-1 POL * (A)

290        300        310        320        330 B      340        350        360
TTC AGG GAT AGC CCC CAT CTA TTT GGC CAG GCA TTA GCC CAA GAC TTG AGT CAA TTC TCA TAC CTG GAC ACT
 F   R   D   S   P   H   L   F   G   Q   A   L   A   Q   D   L   S   Q   F   S   Y   L   D   T>
TRANSLATION OF MSRV-1 POL * (A)

        370        380        390        400        410        420        430
CTT GTC CTT CAG TAC ATG GAT GAT TTA CTT TTA GTC GCC CGT TCA GAA ACC TTG TGC CAT CAA GCC ACC CAA
 L   V   L   Q   Y   M   D   D   L   L   L   V   A   R   S   E   T   L   C   H   Q   A   T   Q>
TRANSLATION OF MSRV-1 POL * (A)

      440        450        460        470        480        490        500
GAA CTC TTA ACT TTC CTC ACT ACC TGT GGC TAC AAG GTT TCC AAA CCA AAG GCT CGG CTC TGC TCA CAG GAG
 E   L   L   T   F   L   T   T   C   G   Y   K   V   S   K   P   K   A   R   L   C   S   Q   E>
TRANSLATION OF MSRV-1 POL * (A)

    510        520        530        540        550        560        570
ATT AGA TAC TNA GGG CTA AAA TTA TCC AAA GGC ACC AGG GCC CTC AGT GAG GAA CGT ATC CAG CCT ATA CTG
 I   R   Y   X   G   L   K   L   S   K   G   T   R   A   L   S   E   E   R   I   Q   P   I   L>
TRANSLATION OF MSRV-1 POL * (A)

    580        590        600        610        620        630        640
GCT TAT CCT CAT CCC AAA ACC CTA AAG CAA CTA AGA GGG TTC CTT GGC ATA ACA GGT TTC TGC CGA AAA CAG
 A   Y   P   H   P   K   T   L   K   Q   L   R   G   F   L   G   I   T   G   F   C   R   K   Q>
TRANSLATION OF MSRV-1 POL * (A)

650        660        670        680        690        700        710        720
ATT CCC AGG TAC ASC CCA ATA GCC AGA CCA TTA TAT ACA CTA ATT ANG GAA ACT CAG AAA GCC AAT ACC TAT
 I   P   R   Y   X   P   I   A   R   P   L   Y   T   L   I   X   E   T   Q   K   A   N   T   Y>
TRANSLATION OF MSRV-1 POL * (A)

        730        740        750        760        770        780        790
TTA GTA AGA TGG ACA CCT ACA GAA GTG GCT TTC CAG GCC CTA AAG AAG GCC CTA ACC CAA GCC CCA GTG TTC
 L   V   R   W   T   P   T   E   V   A   F   Q   A   L   K   K   A   L   T   Q   A   P   V   F>
TRANSLATION OF MSRV-1 POL * (A)

      800        810        820        830        840        850        860
AGC TTG CCA ACA GGG CAA GAT TTT TCT TTA TAT GCC ACA GAA AAA ACA GGA ATA GCT CTA GGA GTC CTT ACG
 S   L   P   T   G   Q   D   F   S   L   Y   A   T   E   K   T   G   I   A   L   G   V   L   T>
TRANSLATION OF MSRV-1 POL * (A)

    870        880        890        900        910        920        930
CAG GTC TCA GGG ATG AGC TTG CAA CCC GTG GTA TAC CTG AGT AAG GAA ATT GAT GTA GTG GCA AAG GGT TGG
 Q   V   S   G   M   S   L   Q   P   V   V   Y   L   S   K   E   I   D   V   V   A   K   G   W>
TRANSLATION OF MSRV-1 POL * (A)

    940        950        960        970        980        990       1000
CCT CAT NGT TTA TGG GTA ATG GNG GCA GTA GCA GTC TNA GTA TCT GAA GCA GTT AAA ATA ATA CAG GGA AGA
 P   H   X   L   W   V   M   X   A   V   A   V   X   V   S   E   A   V   K   I   I   Q   G   R>
TRANSLATION OF MSRV-1 POL * (A)

1010       1020       1030       1040       1050       1060       1070       1080
GAT CTT NCT GTG TGG ACA TCT CAT GAT GTG AAC GGC ATA CTC ACT GCT AAA GGA GAC TTG TGG TTG TCA GAC
 D   L   X   V   W   T   S   H   D   V   N   G   I   L   T   A   K   G   D   L   W   L   S   D>
TRANSLATION OF MSRV-1 POL * (A)

        1090       1100       1110       1120       1130       1140       1150
AAC CAT TTA CTT AAN TAT CAG GCT CTA TTA CTT GAA GAG CCA GTG CTG NGA CTG CGC ACT TGT GCA ACT CTT
 N   H   L   L   X   Y   Q   A   L   L   L   E   E   P   V   L   X   L   R   T   C   A   T   L>
TRANSLATION OF MSRV-1 POL * (A)

AAA CCC
 K   P>
```

FIG. 9 SEQ ID NO 1 (MSRV-1 pol*)

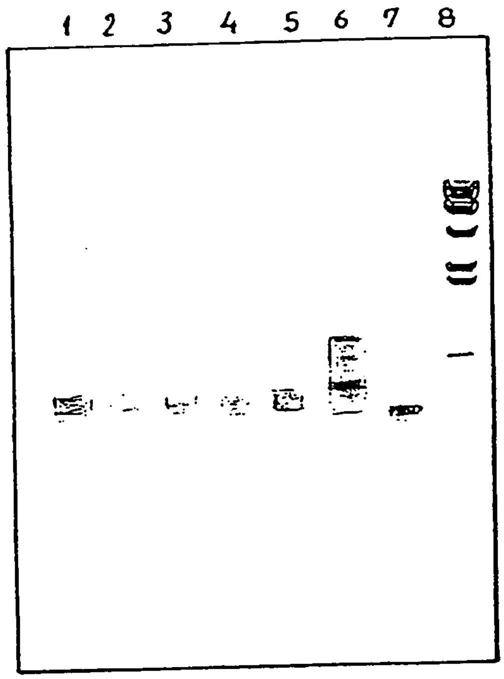


FIG. 10

FIG. 11

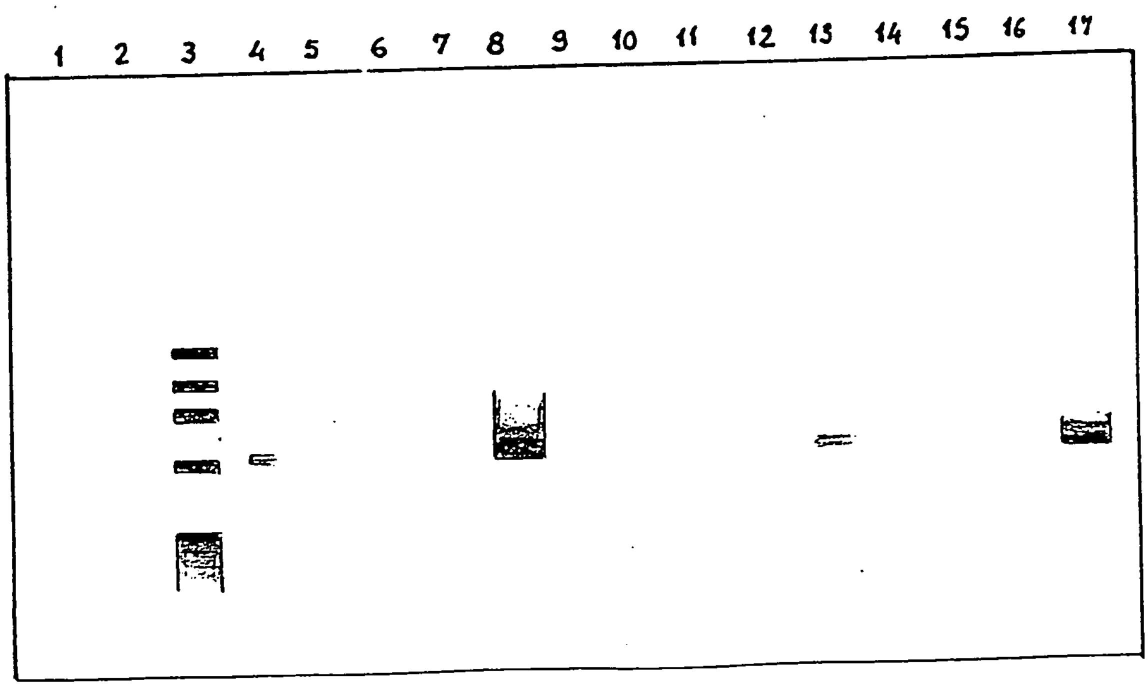


FIG. 12

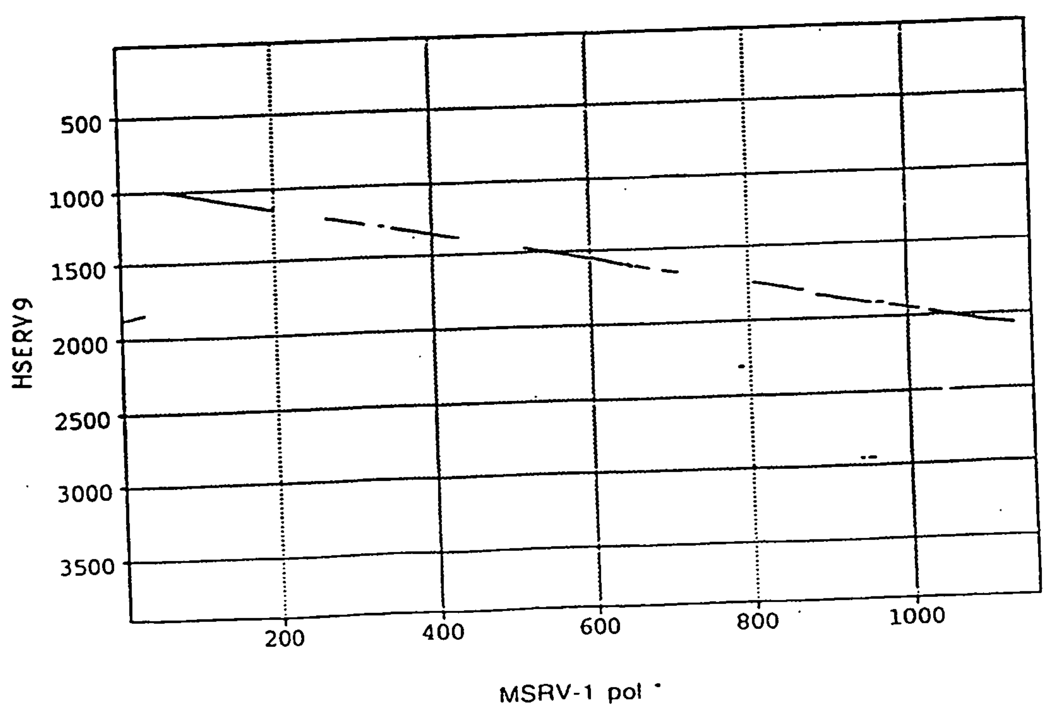

500
1000
1500
2000
2500
3000
3500
HSERV9
200
400
600
800
1000
MSRV-1 pol

FIG. 13

SEQ ID NO 46 (FBd3)

GTGCTGATTGGTGTATTTACAATCCTTTATCTAATCCGAAATGCCCATGTTG
CAATATGGAAAGAAAGGGAGTTCCTAACCTCTGGGGGAACCCCCATTAAA
TACCACAAGTAAATCATGGAGTTATTGCACACAGTGCAAAAACTCAAGGA
GGTGGAAGTCTTACACTGCCAAAGCCATCAGAAAAGGGAAGAGGGGAGAA
GAGCAGCATAAGTGGCTACAGAGGCAAGGAAAGACTAGCAGAAAGGAAA
GAGAGAAAGAGACAGAAAGTCAGAGAGAGAGAGAGGAAGAGACAGAGCA
CAAAGAGGGAGTCAGAGAGAGAGAGAGACAGAGAGTCAGAGAGAAGGAA
AGAGAGAGAGGAAGAGACAAAGAATGAATCAAACAGAGAGACAGAAAGT
CAGAGAGAGAGAGAGAGAGGAAGAGACAGAGAAAAAGAGGGAGTCAGAA
AAAGAGAGACCAAAGAAGAAGTCCAAAGAGAAAGAAAGAGAGATGGAAG
TAGTAAAGGAAAAACAGTGTACCCTATTCCTTTAAAAGCCGGGGTAAATTT
AAAACCTATAATTGATAACTGAAGGTCTTCTCTGTAACCCTGTAACACTCC
AATACCACCTTGTTGTCAAGTGTAAACAAGGGCGTAGCCCAAAAGCACTG
AGGCCACTAACAACCCATAGCCTTCCTATCAAAATTCCTTAACCCAGCAGG
TTTCCTAACAGGGGATCTAAATCTTAATTAATTACCATACAATGGTCCAAC
CAGACTTAGGAGGAATTCCCTTCAGGACGGGAAGATAGATGCTTCCTCCCA
GGCGATTAAGGGAGAAAGACACAATGGGTATTCAGTAAGTGCCAAGGGGA
ACACTTGTAGAAGCAAAGTTAGGAAAATTGCCAAATAATTGGTTTGCTCAA
GAGTTGTTTGCACTCAGCCAAACCTTGAAGTACTTGCAGAATCAGAAAGGA
GCCATCTATACCAATTCTAAGTTAATATGGACTGAAGGAGGTTTTATTAAT
ACCAAAGAGAAATTAAAATCCCAAACTTATAAGGTTTTCAACCAAAGTAA
AGTTTGCTAAAAGTTAACAGCGTAACATGTATTATCCTACTACCACACACT
CTCAAAGGATTTCTCAGACAGTTTGCAAGAAATAATGATATCTATCCTTAC
TCTACAATCCCAAATAGACTCTTTGGCAGCAGTGACTCTCCAAAACCGTCA
AGGCCTAGACCTCCTCACTGCTGAGAAAGGAGGACTCTGCACCTTCTTAAG
GGAAGAGTGTTGTCTTTACACTAACCAGTCAGGGATAGTATGAGATGCTGC
CCGGCATTTACAGAAAAAGGCTTCTGAAATCAGACAACGCCTTTCAAATTC
CTATACCAACCTCTGGAGTTGGGCAACATGGTTTCTTCCCTTTCTATGTCCC
ATGGCTGCCATCTTGCTATTACTCGCCTTTGGGCCCTGTATTTTTAACCTCC
TTGTCAAATTTGTTTCTTCTAGGATCGAGGCCATCAAGCTACAGATGGTCTT
ACAAATGGAACCCCAAATGAGCTCAACTATCAACTTCTACTGAGGACCCCT
AGACCAACCCCCTGGCCCTTTCACTGGCCTAAAGAGTTCCCGTCTGGAGGA
CACTACCACTGCAGGGCCCCATCTTTGCCCCTATCCAGAAGGAAGTAGCTA
GAGCAGTCATTGCCCAATTCCCAAGAGCAGCTGGGGTGTCCCGTTTAGAGT
GGGGATTGAGAGGTGAAGCCAGCTGGACTTCTGGGTCGGGTGGGGACTTG
GAGAACTTTTGTGTCTAGCTAAAGGATTGTAAATGCAACAATCAGTGCTCT
GTGTCTAGCTAAAGGATTGTAAATACACCAATCAGCAC

FIG. 14

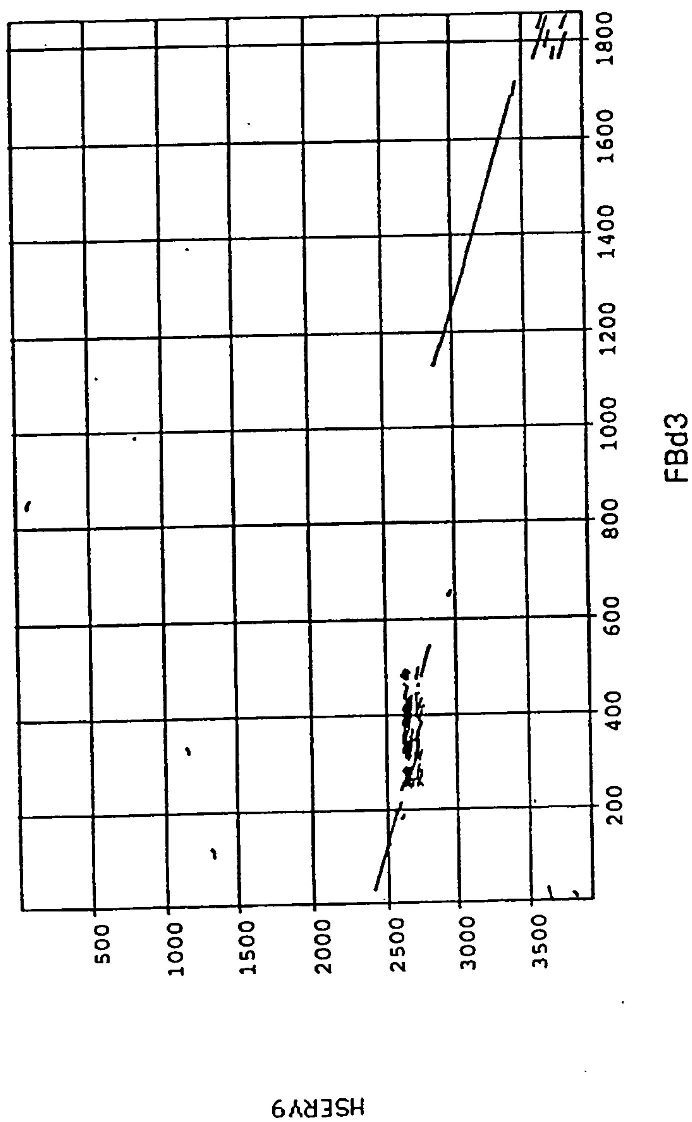

500
1000
1500
2000
2500
3000
3500
200
400
600
800
1000
1200
1400
1600
1800
FBd3
HSERY9

FIG. 15

SEQ ID NO 51 (t pol)

GGCTGCTAAAGGAGACTTGTGGTTGTCAGACAATCGCCTACTTAGGTACCA
GGCCTTATTACTTGAGGGACTGGTGCTTCAGATGCGCACTTGTGCAGCTCT
TAACCCAAACTTATGCTGCCCAGAAGGATCTTTTAGAGGTCCCCTTAGCCA
ACCCTGACCTCAACCTATATATATATACTGATGGAAGTTCGTTTGTAGAAAAG
GGATTACAAAGGGNAGGATATNCCATAGGTTAGTGATAAAGCAGTACTTG
AAAGTAAGCCTCTTCCCCCCAGGGACCAGCGCCCCCGTTAGCAGAACTAGT
GGCACTGACCCCGAGCCTTAGAACTTGGAAAGGGAGGAGGATAAATGTGT
ATACAGATAGCAAGTATGCTTATCTAATCCGAAATGCCCATGTTG

SEQ ID NO 52 (JLBc1)

TCAGGGATAGCCCCCATCTATTTGGTCAGGCACTGGCCCAAGATCTAGGGA
CATGCCACTTTTAAGAGCCATTTCTCAAGTCCAGGTACTCTGGTCCTTCGGT
ATGTGGATGATTTACTTTTGGCTACCAGTTCAGTAGCCTCATGCCAGCAGG
CTACTCTAGATCTCTTGAACTTTCTAGCTAATCAAGGGTACAAGGCATCTA
GGTTGAAGGCCCAGCTTTGCCTACAGCAGGTCAAATATCTAGGCCTAATCT
TAGCCAGAGGGACCAGGGCACTCAGCAAGGAACAAATACAGCCTATACTG
GCTTATCCTCACCCTAAGACATTAAAACAGTTGCGGGGGTTCCTTGGAATC
ACTGGCTTTTTGGTGACTATGGATTCCCAGATACAGCAAGATTGGCAGGCC
CCTCTATACTGTAATCAAGGAGACTCACGAGGGCAAGTACTCATCTAGTAG
AATGGGAACTAGGGACAGAAACAGCCTTCAAAACCTTAAAGCAGGCCCTA
GTACAATCTCCAGCTTTAAGCCTTCCCACAGGACAAAACTTCTCTTTATAC
ATCACAGAGAGGGCAGAGATAGCTCTTGGTGTCCTTATTCAGACTCATGGG
ACTACCCCACAACCAGTGGCACACCTAAGTAAGGAAATTGATGTAGTAGC
AAAAGGCTGGCCTCACTGTTTATGGGTAGCTGTGGTGGTGGCTGTCTTAGT
GTCAGAAGCTATCAAAATAATACAAGGAAAGGATCTCACTGTCTGGACTA
CTCATGATGTAATGGCATACTAGGTGCCAAAAGAAGTTTATGGGTATCAGA
CAACCACCTGCTTAGATACCAGGGACTACTCCTGGAGGATTGGGCTTCAAG
TGCGTTTTTTGTGGCCTCAACCCTGCCACTTTTCCTCCAGAGGATGGAGAG
CCGCTTGAGCATGCTTGCCAACAGGTTGTAGGCCAGAATTATTCCACCCGA
GATGATCTCTTAGAGTACCCTTAGCTAATCCTGACCTTAACCTATATACCA
ATGGAAGTTCATTTGTGGAAAACGGGATATGAAGGGCAGGTTATGTCATAG
TTAGTGATGTAATCATACTTGCAAGTAAGCCTCTTACCCCAGGGGCCAGCA
CTCAGTTAGCAGAACTAGTCACACTTACCTTAACCTTAGAACTGGGAAAGG
GAAAAAGAATAAATATGTATACAGATAGTAAGTATGCTTATCTAATCCTAC
ATGCCCATGCTGCAATATGGAAGGAAAGGGAGTTCCTAACCCCTGGGGGA
ACCCCCATTAAATACCACAAGGYAAATCATGGAGTTATTGCACGCAGTGC
AAAAACTCAAGGAGGTGGCAGTCTTACACTGCCGAAGCYATCAAAAAGGG
GAAGGAGAGGGGAGAACAGCAGCATAAGTGGTTGGCAGAGGCAGTGAAA
GACCAGCAGAGAGAAGGAGAGAGACAACGTCAACGACAGAAGGAAAGAA
GAGGAGGAGACAGAGAGGAAGAGACAGAGAGACAGTTAGTCCAAGAGAG
AGACAGAGAGAGGAAGAGACAGACAGAAAGTCCAAGAGAGAAGGAAAGA
GAGGAAGAGACCAAGGAGTCCNAGAGAGAGAAAGAGATAGAAGTAGTAA
AGAAAAAACATTGTACCCTATTCCTTTAAAAGCCGGGGTATATTTAAAACC
TATAATTGATAATTGAGTTCTTGCACCCTCCTCCAGGGGATYGCTGGGAGG
AAACCCTCAACCGATATGTGAAAATTGTGGGTCGTCCCTATGTCTCAATTA
CCAGCCAATACCCCCTTGTTTTTAGTGTGAACGAGGGTGTAGAGCGCAGAC
AGGGAGACCTCTGACAATCCATACCCTTCCTATCCAAAATCCTTAACCCAG
CAGGTTTTCTAAAAGGGGATCTAAATCTTAATTAATTACCATACAAAGGTC
AAACCAGATCTAGGAGGAACTTCCTTCAGGACAGGATGATAGATGGTTCCT
CCCAGGCGATTAAAGAAAATAAAAAGACACATGGGCAGCCAGTAAGTGAT
AAGGGAACACTAGTAGAAGCAGTTAGGAGAAGTTGCCTAATAATTGGTCT
ACTCCAAATGTGTGAGTTGTTCGCACTCAGCCCAAATCTTAAAGTACTTAC
AGAATTAGGGAGGAGCCATTTACACCAATTCTAAGTTAATATGGACTGGAT
GAGGTTTTATTAATAGCGAAGGAGAATTAAATCCTAAACTNACAAGGTTTT
CAACTAAAGTAAATTTTACTAAAAGCTAACAGTGTAACATGCATTATCCTA
CTACAACACACTCTCANAGGATTCCTCAGACAGTTTACAAGAAATAACAA
AATCTATCTGGTAAGGATAGTAACTACAATCCCAAATACATTCTTTGGCAG
CAGTGACTCTC

FIG.16

SEQ ID NO 53 (JLBc2)

TCAGGGATAGCCCCCATCTATTTGATCAGGCACTAGCCCAAGATCTAGGCC
ACTTCTGAAGTCCAGGCATTCTAGTCCTTCAGTATGTGGATGATTTACTTTT
GGCTACCAGTTTGGAAGCCTCATGCCAGCAGGCTACTTGAGATCTCTTGAA
CTTTCTAGCTAATCAAGGGTGTATGGCATCTAAATTGAAAGTCCAGCTCTG
CCTACAACAAGTCAAATATCTAGGCCTAATCTTAGATAGAAGAACCAGGG
CCCTCAGCAAGGAATGAATAAAGCCTATGCTGGCTTATCGGCACCCTAAGA
CATTAAAACAATTGTGGGGGTTCCTTGGAATCACTGGCTTTTGCCGACTAT
GGATCCCTGGATAGAGTGAGATAGCCAGGCCCCCTCTATTACTCTTATCAA
GGAGACCCAGAGGGCAAATACTTATCTAGTATTATGGGNACCAGAGGCAG
AAAAAGCCTTCCAAACCTTAAAGGAGACCCTAGTACAAGCTCCAGCTTTAA
GCCTTCCCACAGGACAAANCTTCTCTTTATATGTCACAGAGAGAGCAGGAA
TAGCTCCTGGAGTCCTTACTCAGACTTTTGGACGACCCCACGGCCAGTGGC
RTACCTAAGTAAGGAAATTGATGTAGTAGCAAAAGGCTGGCCTCACTGTTT
ATGGGTAGTTGCGGCTGTGGCAGTCTTACTGTCAAAGGCTATCAAAATAAT
ACAAGGAAAGGATTTCACTATCTGGACTACTCATGAGGAAAATGGCATATT
AGGTGCCAAAGGAAGTTTTTGGCTATCAGACAACCACCTGCTCAGATTCCA
GGCACTACTGATTGAGAGACCAGTGCTTTAAATATGTATGTGTGTGTGTGG
CCCTCAACCCTGCCACTGTTCTCCCAGAAGATGGAGAACCAATGAAGCATT
ACTGTCAACAAATTAGAGTCCAGAGTTATGCTGCCTGAGAGGATCTCTTAG
AAGTCCCCTTAGCTAATCCTGACCTTAACCTATATGCTGATGGAAGTTCAC
TTGTGGAGAATGGGATACGAAAAGCACATTATGCCATAGTTAGTGAGGTA
ACAGTACTTGAAAGTAAGCCTATTCCCCCATGGACCAGAGCCCAGTTAGCA
GAACTAGTGGCACTTACCCAAGCCTTAGAACTAGGAAAGGGAAAAATAAT
AAATGTGTATACAGATAGCAAGTATGCTTATCTAATCCTACATGCCCATGC
TGCAGTATGGAAAGAAAGGGAGTTCCTAACCTCTGGGGGAACCCCCATTA
AATACCACAAGGCAAATCATGGAGTTATTGCATGTAGTGCAAAACCTCAA
GTAGGTGGCAGTTTTACACTGCCTGAAGCTATGGGGAAGGAGAGAGGAGA
ACAGCAGCATAAGTGGCTAGCAGAGGCAGCGAAAGACTAGCAGAGAGGA
GAGGTAGGGGAAAGACAGAAAGTCAAAGAAAAGAAGTCAAAGACAGACA
GAGAAAGAGACAGAGGGAGCCAGAGAGAAAGAAAAGAGAGAACGAAAGA
GACAGAATGTCAAAGAACAGAAGAGAGAGGCAGCGCCAGAAGAGTTAAG
AAAGTGAGAAAGAGAGATGGAAATAGTAAAGAAAAAACAGTGTACCCTAT
TCCTTTAAAAGCCAGGGTAAATTTAAAACGTATAATTTTATAATTGGAAGG
TCTTCTCCATAACCCTATAACATTAAAATACCACCTTGTTGTCAGTGTAAAC
AAGAGCATAGCCCAAAAGCACTGAGGCCACTGACAACCCATAGCCTTCCT
ATCAAAAATCCTTAACTCTGCAGGTTTCCTAACAGGGGATCTAAATCTCAA
CTAATCACCATACAATGGTCCGACCAGACCTAGGAGCGACTCCCCTCAGG
ACAGAAGGATGGATGGTTCCTCCCAGGCCATTAAGGGAAAGAGACACAAT
GGGTATTCAGTAAGTGATAAGGGAACTCTTGTAGAAGCAGTTAGGAAGATT
GCCTAATATTTGGTCTGCTCAAATGTGCCAGCTGTTTGCACTCAGCTAAAC
CTTAAATTACTTACAGAATTAGGAAGGAGCCATCTATACCAATTCTGAGTT
AATATGAGCTGAACAAGTTCTTATTAATAGCAAAGAATCATTGAAATCTCA
AACTTGCAAAGTTTTCAACAAAAGTAAAGTTTGCTGAAAGTTAGCAGTGTA
ACATGTATTATCCTAACTTCTAATCTTGTGGAAATCAGACCCTATCAGTGC
CCCTCAAAGCTGAAGTCCATCAGCATATGGCCATACAACTAATACCCCTAT
TTATAGGGTTAGGAATGGCCACTGCTACAGGAATGGGAGTAACAGGTTTAT
CTACTTCATTATCCTATTACCACACACTCTTAAAGGATTTCTCAGACAGTTT
ACAAGAAATAACAAAATCTATCCTTACTCTNTARTCCCAAATAGRTTCTTT
GGCAGCAGTGACTCTC

FIG. 17

FIG 18

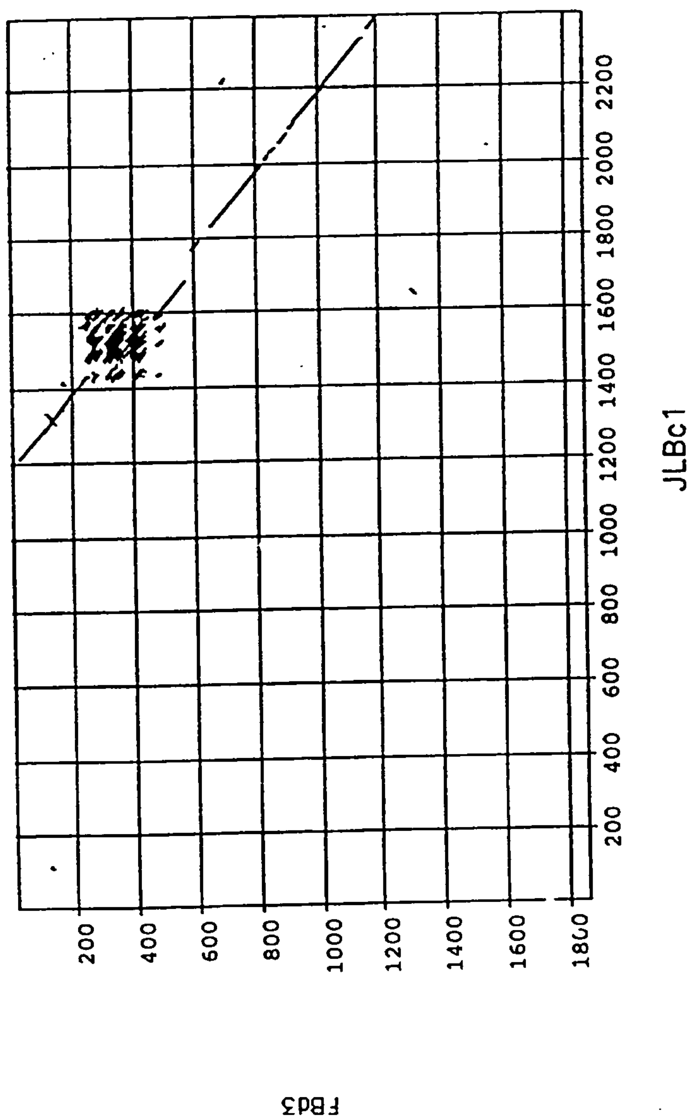
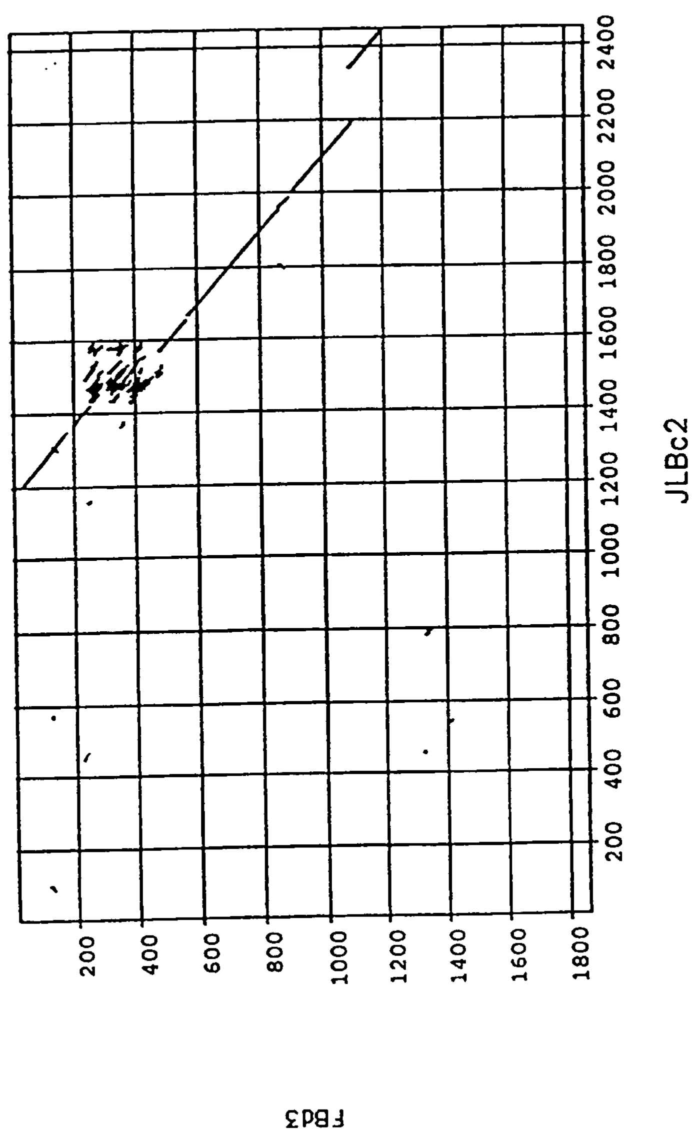

200 400 600 800 1000 1200 1400 1600 1800 2000 2200
JLBc1
200 400 600 800 1000 1200 1400 1600 1800
FBd3

FIG 19



200 400 600 800 1000 1200 1400 1600 1800 2000 2200 2400
JLBc2
200 400 600 800 1000 1200 1400 1600 1800
FBd3

FIG 20

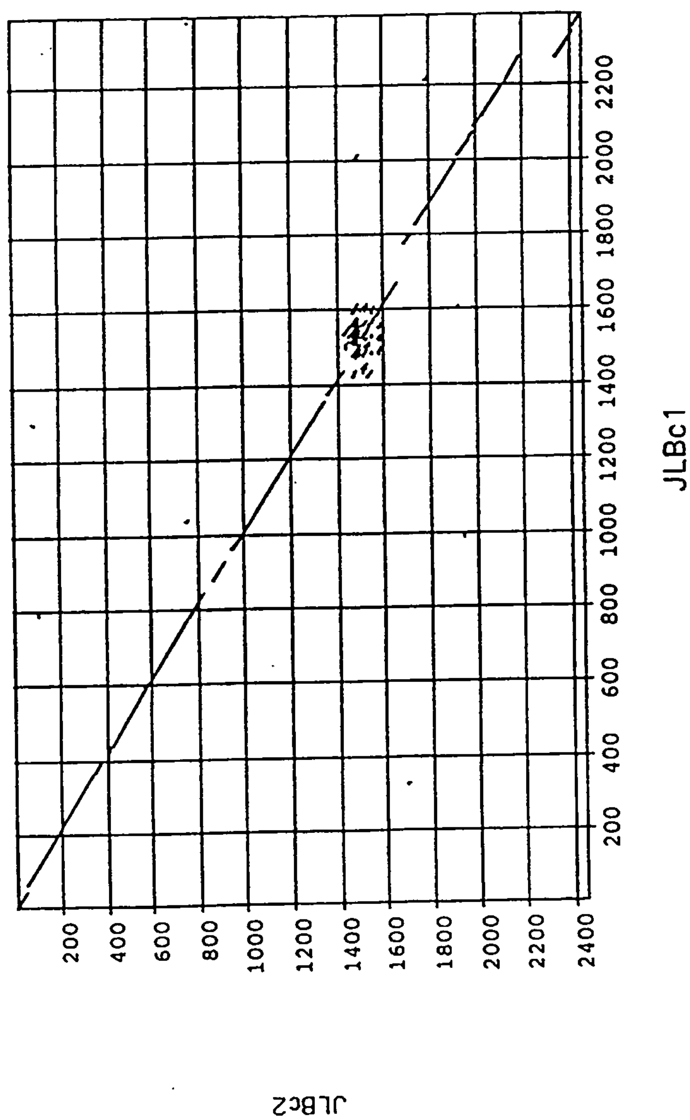

JLBc1
JLBc2
200 400 600 800 1000 1200 1400 1600 1800 2000 2200
200 400 600 800 1000 1200 1400 1600 1800 2000 2200 2400

FIG 21

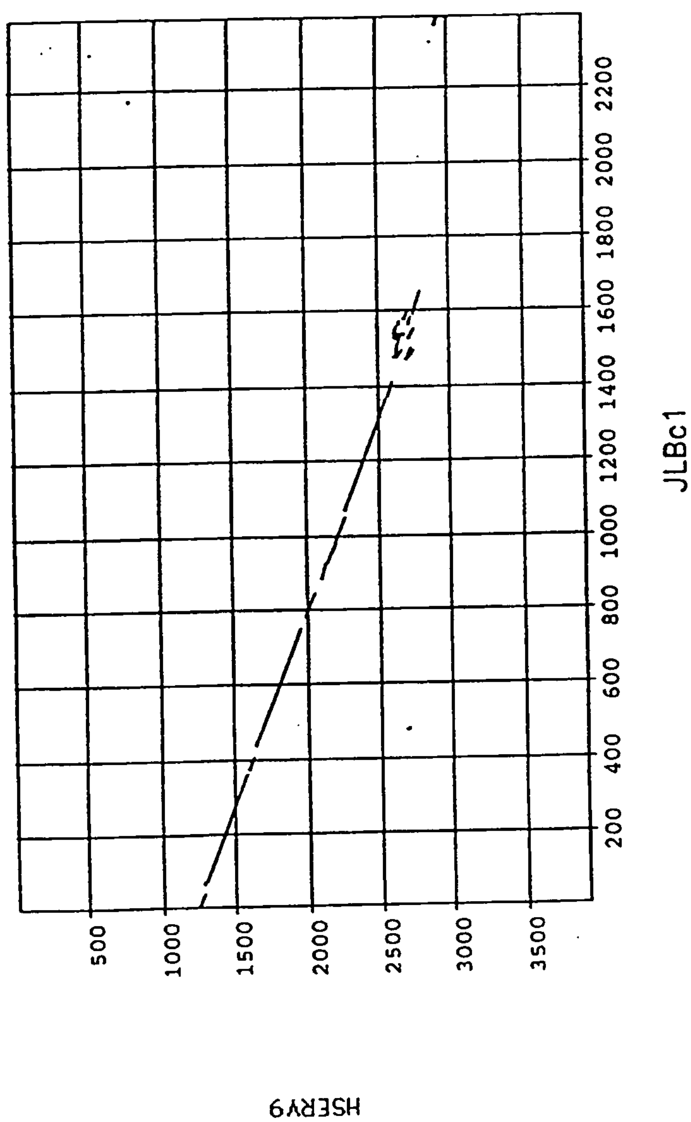
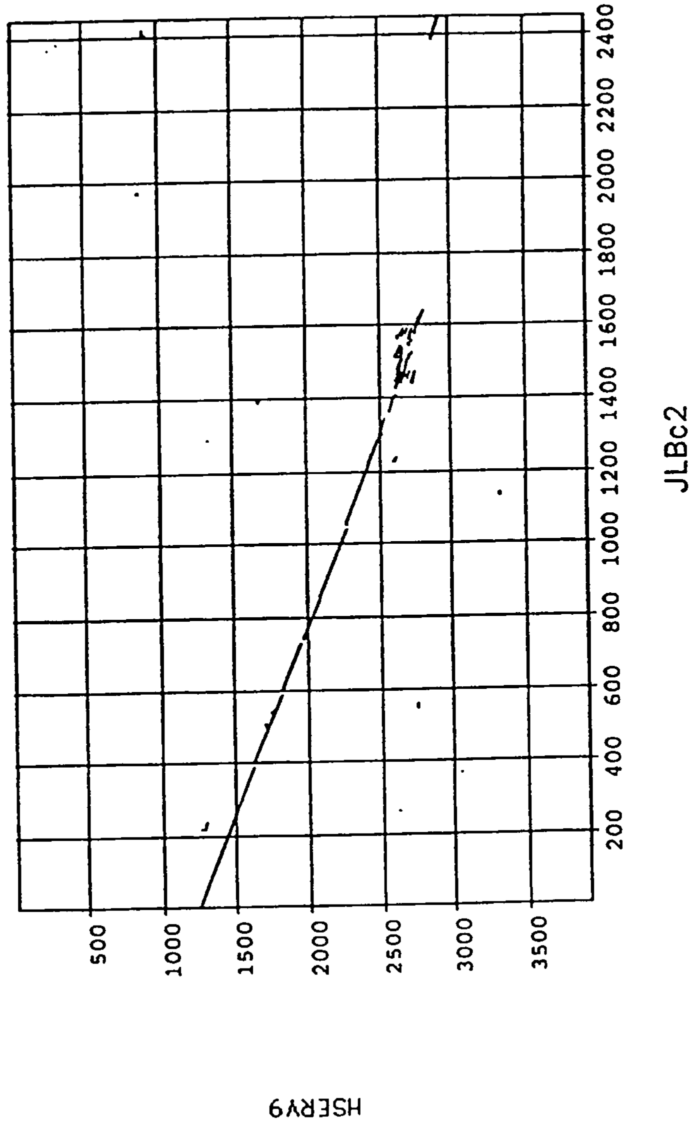

200
400
600
800
1000
1200
1400
1600
1800
2000
2200
JLBc1
500
1000
1500
2000
2500
3000
3500
HSERY9

FIG 22


200 400 600 800 1000 1200 1400 1600 1800 2000 2200 2400
JLBc2
500 1000 1500 2000 2500 3000 3500
HSERY9

```
   1 TTCCTGAGTT CTTGCACTAA CCTCAAATGA GAGAAGTGCC GCCATAACTG CAACCCAAGA
  61 GTTTGGCGAT CCCTGGTATC TCAGTCAGGT CAATGACAGG ATGACAACAG AGGAAAGATA
 121 ATGATTCCCC ACAGGCCAGC AGGCAGTTCC CAGTGTAGAC CCTCATTAGG ACACAGAATC
 181 AGAACATGGA GATTGGTGCC GCAGACATTT GCTAACTTGC GTGCTAGAAG GACTAAGGAA
 241 AACTAGGAAG ATATGAATTA TTCAATGATG TCCACTATAA CACAGGGGAA AGGAAGAAAA
 301 TCCTACTGCC TTTCTGGAGA GACTAAGGGA GGCATTGAGG AAGCATACCA GGCAAGTGGA
 361 CATTGGAGGC TCTGGAAAAG GGAAAAGTTG GGAAAAGTAT ATGTCTAATA GGGCTTGCTT
 421 CCAGTGTGGT CTACAAGGAC ACTTTAAAAA AGATTGTCCA ATAGAAATAA GCCACCACCT
 481 CGTCCATGCC CCTTATGTCA AGGGAATCAC TGGAAGGCCC ACTGCCCCAG GGGATGAAGG
 541 TCCTCTGAGT CAGAAGCCAC TAACCAGATG ATCCAGCAGC AGGACTGAGG GTGCCCGGGG
 601 CAAGCGCCAG CCCATGCCAT CACCCTCACA GAGCCCCAGG TATGCTTGAC CATTGAGGGT
 661 CAGAAGGGTA CTGTCTCCTG GACACTGGCG GGCCTTCTCA GTCTTACTTT CCTGTCCTGG
 721 ACAACTGTCC TCCAGATCTG TCACTGTCCG AGGGGTCCTA GGACAGCCAG TCACTAGATA
 781 CTTCTCCCAG CCACTAAGTT GTGACTGGGG AACTTTACTC TTCCACATGC TTTTCTAATT
 841 ATGCCTGAAA GCCCCACTCT CTTGTTAGGG GAGAGACATT CTAGCAAAAG CAGGGGCCAT
 901 TATACATGTG AATATAGGAG AAGGAACAAC TGTTTGTTGT CCCCTGCTTG AGGAAGGAAT
 961 TAATCCTGAA GTCCGGGCAA CAGAAGGACA ATATGGACAA GCAAAGAATG CCCGTCCTGT
1021 TCAAGTTAAA CTAAAGGATT CCACCTCCTT TCCCTACCAA AGGCAGTACC CCCTCAGACC
1081 CGAGACCCAA CAAGAACTCC AAAAGATTGT AAAGGACCTA AAAGCCCAAG GCCTAGTAAA
1141 ACCAAGCAAT AGCCCTTGCA AGACTCCAAT TTTAGGAGTA AGGAAACCCA ACGGAC
```

SEQ ID NO 56 (GM3)

FIG. 23

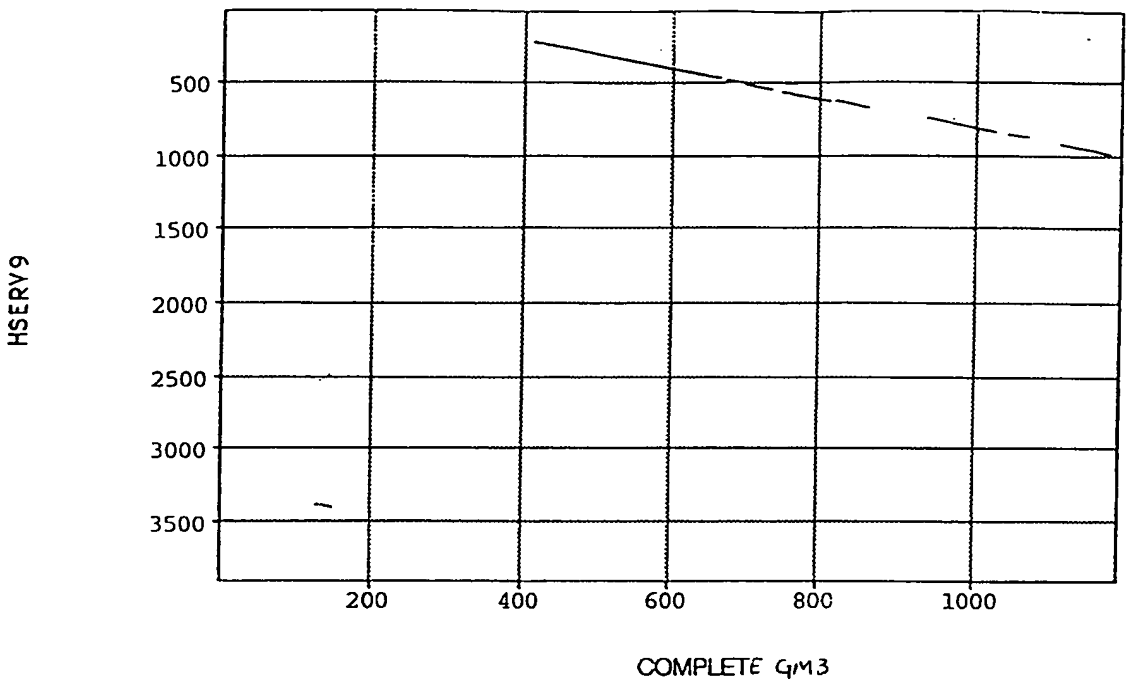
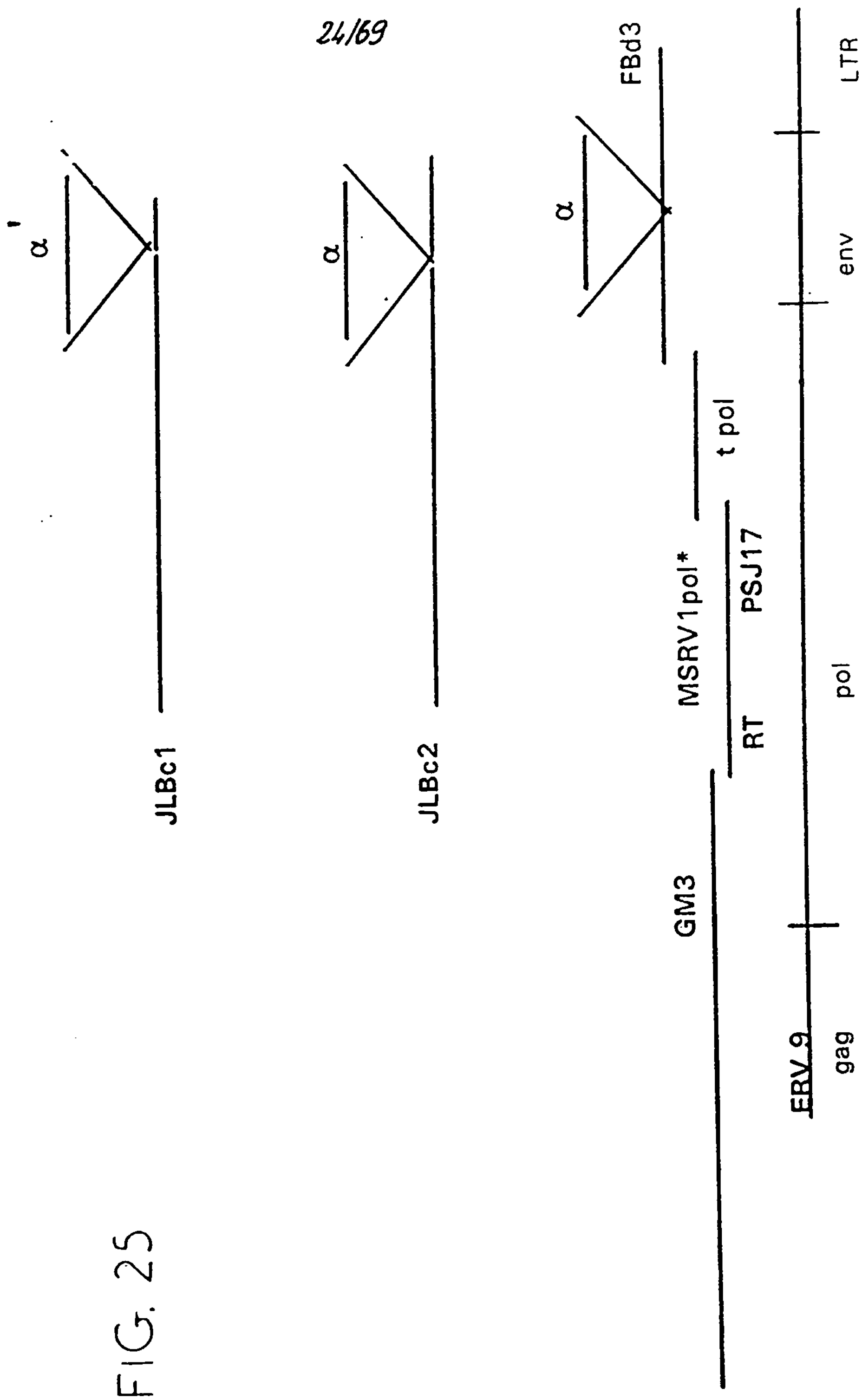

HSERV9
500
1000
1500
2000
2500
3000
3500
200
400
600
800
1000
COMPLETE GM3

FIG. 24



α'
JLBc1
α
JLBc2
α
FBd3
t pol
MSRV1pol*
PSJ17
RT
GM3
ERV 9
LTR
env
pol
gag

FIG. 25

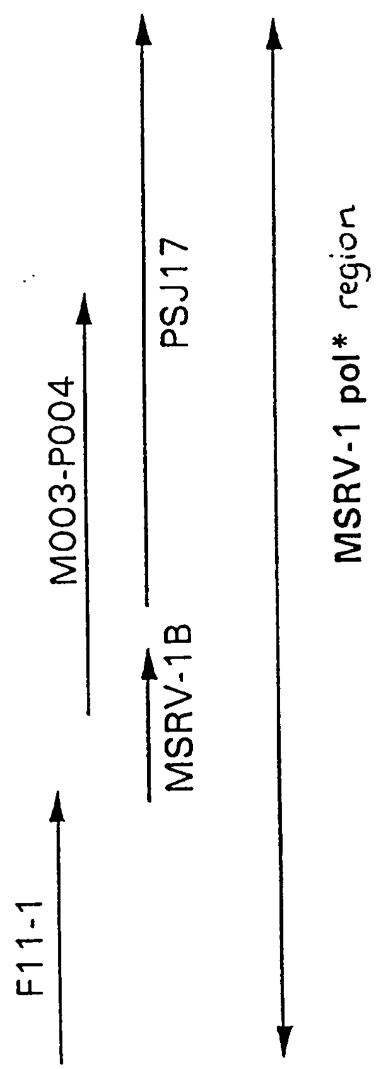


FIG. 26

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FIG. 27a

SEQ ID NO 57 (POL)

```
ATG ATC CAG CAG CAG GAC NGA GGG TGC CCG GGG CAA GCG CCA GCC CAT GCC ATC ACC CTC ACA GAG CCC CAG GTA TGC TTG ACC ATT GAG   90
 M   I   Q   Q   Q   D   X   G   C   P   G   Q   A   P   A   H   A   I   T   L   T   E   P   Q   V   C   L   T   I   E

GGT CAG AAG GGT NAC TGT CTC CTG GAC ACT GGC GGN GCC TTC TCA GTC TTA CTT TCC TGT CCT GGA CAA CTG TCC TCC AGA TCT GTC ACT   180
 G   Q   K   G   X   C   L   L   D   T   G   G   A   F   S   V   L   L   S   C   P   G   Q   L   S   S   R   S   V   T

GTC CGA GGG GTC CTA GGA CAG CCA GTC ACT AGA TAC TTC TCC CAG CCA CTA AGT TGT GAC TGG GGA ACT TTA CTC TTC CCA CAT GCT TTT   270
 V   R   G   V   L   G   Q   P   V   T   R   Y   F   S   Q   P   L   S   C   D   W   G   T   L   L   F   P   H   A   F

CTA ATT ATG CCT GAA AGC CCC ACT CTC TTG TTG GGG AGA GAC ATT CTA GCA AAA GCA GGG GCC ATT ATA CAT GTG AAT ATA GGA GAA GGA   360
 L   I   M   P   E   S   P   T   L   L   L   G   R   D   I   L   A   K   A   G   A   I   I   H   V   N   I   G   E   G

ACA ACT GTT TGT TGT CCC CTG CTT GAG GAA GGA ATT AAT CCT GAA GTC CGG GCA ACA GAA GGA CAA TAT GGA CAA GCA AAG AAT GCC CGT   450
 T   T   V   C   C   P   L   L   E   E   G   I   N   P   E   V   R   A   T   E   G   Q   Y   G   Q   A   K   N   A   R

CCT GTT CAA GTT AAA CTA AAG GAT TCC ACC TCC TTT CCC TAC CAA AGG CAG TAC CCC CTC AGA CCC GAG ACC CAA CAA GAA CTC CAA AAG   540
 P   V   Q   V   K   L   K   D   S   T   S   F   P   Y   Q   R   Q   Y   P   L   R   P   E   T   Q   Q   E   L   Q   K

ATT GTA AAG GAC CTA AAA GCC CAA GGC CTA GTA AAA CCA AGC AAT AGC CCT TGC AAG ACT CCA ATT TTA GGA GTA AGG AAA CCC AAC GGA   630
 I   V   K   D   L   K   A   Q   G   L   V   K   P   S   N   S   P   C   K   T   P   I   L   G   V   R   K   P   N   G

CAG TGG AGG TTA GTG CAA GAA CTC AGG ATT ATC AAT GAG GCT GTT GTT CCT CTA TAC CCA GCT GTA CCT AAC CCT TAT ACA GTG CTT TCC   720
 Q   W   R   L   V   Q   E   L   R   I   I   N   E   A   V   V   P   L   Y   P   A   V   P   N   P   Y   T   V   L   S

CAA ATA CCA GAG GAA GCA GAG TGG TTT ACA GTC CTG GAC CTT AAG GAT GCC TTT TTC TGC ATC CCT GTA CGT CCT GAC TCT CAA TTC TTG   810
 Q   I   P   E   E   A   E   W   F   T   V   L   D   L   K   D   A   F   F   C   I   P   V   R   P   D   S   Q   F   L

TTT GCC TTT GAA GAT CCT TTG AAC CCA ACG TCT CAA CTC ACC TGG ACT GTT TTA CCC CAA GGG TTC AGG GAT AGC CCC CAT CTA TTT GGC   900
 F   A   F   E   D   P   L   N   P   T   S   Q   L   T   W   T   V   L   P   Q   G   F   R   D   S   P   H   L   F   G

CAG GCA TTA GCC CAA GAC TTG AGT CAA TTC TCA TAC CTG GAC ACT CTT GTC CTT CAG TAC ATG GAT GAT TTA CTT TTA GTC GCC CGT TCA   990
 Q   A   L   A   Q   D   L   S   Q   F   S   Y   L   D   T   L   V   L   Q   Y   M   D   D   L   L   L   V   A   R   S

GAA ACC TTG TGC CAT CAA GCC ACC CAA GAA CTC TTA ACT TTC CTC ACT ACC TGT GGC TAC AAG GTT TCC AAA CCA AAG GCT CGG CTC TGC   1080
 E   T   L   C   H   Q   A   T   Q   E   L   L   T   F   L   T   T   C   G   Y   K   V   S   K   P   K   A   R   L   C
```

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FIG. 27b

SEQ ID NO 57 (POL)

```
TCA CAG GAG ATT AGA TAC TNA GGG CTA AAA TTA TCC AAA GGC ACC AGG GCC CTC AGT GAG GAA CGT ATC CAG CCT ATA CTG GCT TAT CCT  1170
 S   Q   E   I   R   Y   X   G   L   K   L   S   K   G   T   R   A   L   S   E   E   R   I   Q   P   I   L   A   Y   P

CAT CCC AAA ACC CTA AAG CAA CTA AGA GGG TTC CTT GGC ATA ACA GGT TTC TGC CGA AAA CAG ATT CCC AGG TAC ASC CCA ATA GCC AGA  1260
 H   P   K   T   L   K   Q   L   R   G   F   L   G   I   T   G   F   C   R   K   Q   I   P   R   Y   X   P   I   A   R

CCA TTA TAT ACA CTA ATT ANG GAA ACT CAG AAA GCC AAT ACC TAT TTA GTA AGA TGG ACA CCT ACA GAA GTG GCT TTC CAG GCC CTA AAG  1350
 P   L   Y   T   L   I   X   E   T   Q   K   A   N   T   Y   L   V   R   W   T   P   T   E   V   A   F   Q   A   L   K

AAG GCC CTA ACC CAA GCC CCA GTG TTC AGC TTG CCA ACA GGG CAA GAT TTT TCT TTA TAT GCC ACA GAA AAA ACA GGA ATA GCT CTA GGA  1440
 K   A   L   T   Q   A   P   V   F   S   L   P   T   G   Q   D   F   S   L   Y   A   T   E   K   T   G   I   A   L   G

GTC CTT ACG CAG GTC TCA GGG ATG AGC TTG CAA CCC GTG GTA TAC CTG AGT AAG GAA ATT GAT GTA GTG GCA AAG GGT TGG CCT CAT NGT  1530
 V   L   T   Q   V   S   G   M   S   L   Q   P   V   V   Y   L   S   K   E   I   D   V   V   A   K   G   W   P   H   X

TTA TGG GTA ATG GNG GCA GTA GCA GTC TNA GTA TCT GAA GCA GTT AAA ATA ATA CAG GGA AGA GAT CTT NCT GTG TGG ACA TCT CAT GAT  1620
 L   W   V   M   X   A   V   A   V   X   V   S   E   A   V   K   I   I   Q   G   R   D   L   X   V   W   T   S   H   D

GTG AAC GGC ATA CTC ACT GCT AAA GGA GAC TTG TGG TTG TCA GAC AAC CAT TTA CTT AAN TAT CAG GCT CTA TTA CTT GAA GAG CCA GTG  1710
 V   N   G   I   L   T   A   K   G   D   L   W   L   S   D   N   H   L   L   X   Y   Q   A   L   L   L   E   E   P   V

CTG NGA CTG CGC ACT TGT CCA ACT CTT AAA CCC AAA CTT ATG CTG CCC AGA AGG ATC TTT NTA GAG GTC CCC TTA GCC AAC CCT GAC CTC  1800
 L   X   L   R   T   C   A   T   L   K   P   K   L   M   L   P   R   R   I   F   X   E   V   P   L   A   N   P   D   L

AAC TAT ATA TAT ACT GAT GGA AGT TCG TTT GTA GAA AAG GGA TTA CAA AGG GNA GGA TAT NCC ATA GGT GTT AGT GAT AAA GCA GTA CTT  1890
 N   Y   I   Y   T   D   G   S   S   F   V   E   K   G   L   Q   R   X   G   Y   X   I   G   V   S   D   K   A   V   L

GAA AGT AAG CCT CTT CCC CCC CAG GGA CCA GCG CCC CCG TTA GCA GAA CTA GTG GCA CTG ACC CCG CGA GCC TTA GAA CTT TGG AAA GGG  1980
 E   S   K   P   L   P   P   Q   G   P   A   P   P   L   A   E   L   V   A   L   T   P   R   A   L   E   L   W   K   G

AGG AGG ATA AAT GTG TAT ACA GAT AGC AAG TAT GCT TAT CTA ATC CGA AAT GCC CAT GTT GTT TAT CTA ATC CGA AAT GCC CAT GTT GCA  2070
 R   R   I   N   V   Y   T   D   S   K   Y   A   Y   L   I   R   N   A   H   V   V   Y   L   I   R   N   A   H   V   A

ATA TGG AAA GAA AGG GAG TTC CTA ACC TCT GGG GGA ACC CCC ATT AAA TAC CAC AAG TTA ATC ATG GAG TTA TTG CAC ACA GTG CAA AAA  2160
 I   W   K   E   R   E   F   L   T   S   G   G   T   P   I   K   Y   H   K   L   I   M   E   L   L   H   T   V   Q   K
```

SEQ ID NO 57 (POL)

```
CTC AAG GAG GTG GAA GTC TTA CAC TGC CAA AGC CAT CAG AAA AGG GAA AGG GGA GAA GAG CAG CAT AAG TGG CTA CAG AGG CAA GGA AAG   2250
L   K   E   V   E   V   L   H   C   Q   S   H   Q   K   R   E   R   G   E   E   Q   H   K   W   L   Q   R   Q   G   K

ACT AGC AGA AAG GAA AGA GAG AAA GAG ACA GAA AGT CAG AGA GAG AGA GAG GAA GAG ACA GAG CAC AAA GAG GGA GTC AGA GAG AGA GAG   2340
T   S   R   K   E   R   E   K   E   T   E   S   Q   R   E   R   E   E   E   T   E   H   K   E   G   V   R   E   R   E

AGA CAG AGA GTC AGA GAG AAG GAA AGA GAG AGA GGA AGA GAC AAA GAA TGA                                                       2391
R   Q   R   V   R   E   K   E   R   E   R   G   R   D   K   E   .
```

FIG. 27c

FIG. 28

GATGCCTTTTTCTGCATCCCTGTACGTCCTGACTCTCAATTCTTGTTTGCCTTTGAAG
ATCCTTTGAACCCAACGTCTCAACTCACCTGGACTGTTTTACCCCAAGGGTTCAGGGA
TAGCCCCATCTATTTGGCCAGGCATTAGCCCAAGATGCCTTTTGCATCCCTGTACGTG
ACTCTCAATTCTTGTTTGCCTTTGCCTTTGAAGATGCTTTGAACCCAACGTCTCAACT
CACCTGGACTGTTTTACGCCAAGGGTTCAGGGATAGCCCCCATCTATTTGGC
CAGGCATTAGCCCAA SEQ ID NO 40

Asp-Ala-Phe-Phe-Cys-Ile-Pro-Val-Arg-Pro-Asp-Ser-Gln-Phe-
Leu-Phe-Ala-Phe-Glu-Asp-Pro-Leu-Asn-Pro-Thr-Ser-Gln-Leu-
Thr-Trp-Thr-Val-Leu-Pro-Gln-Gly-Phe-Arg-Asp-Ser-Pro-His-
Leu-Phe-Gly-Gln-Ala-Leu-Ala-Gln

SEQ ID NO 39 (POL2B)

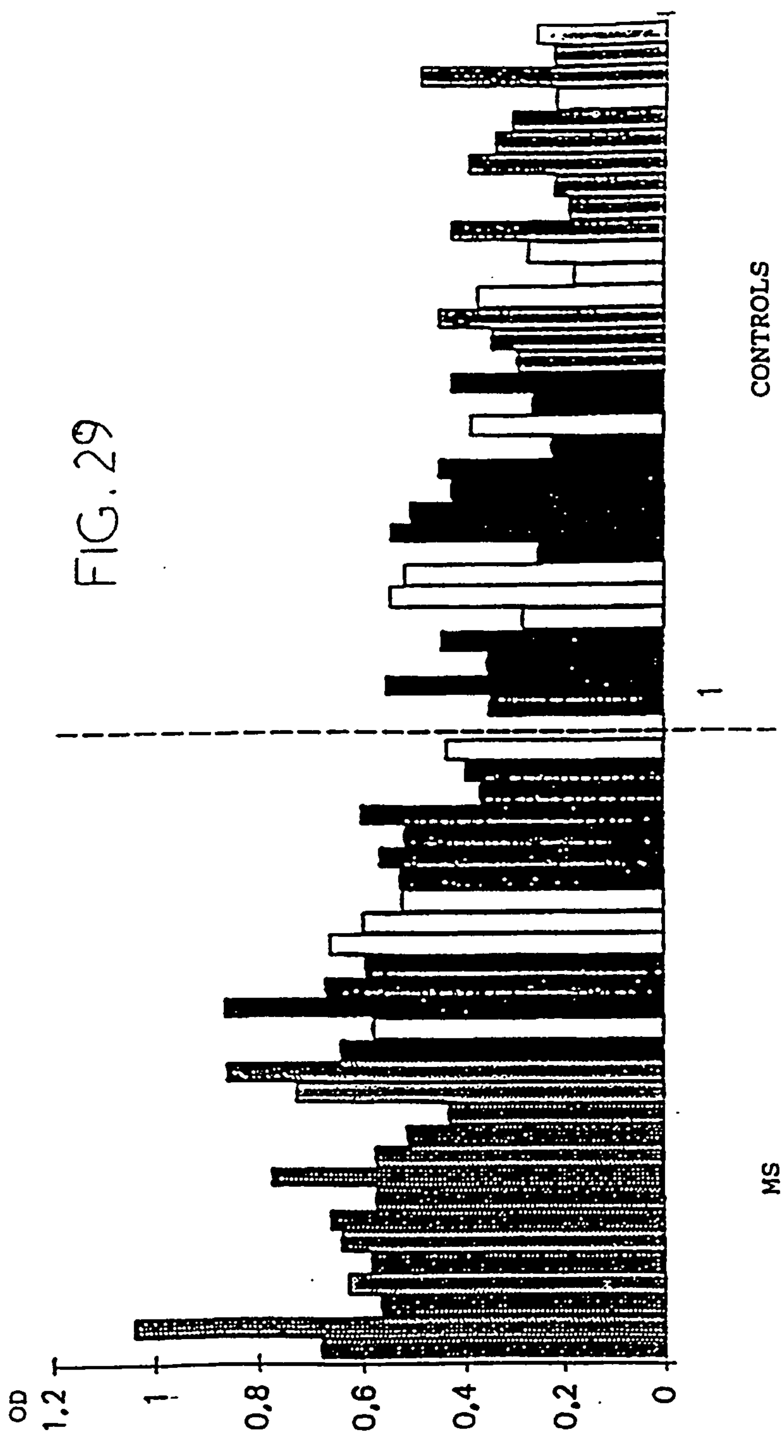


FIG. 29

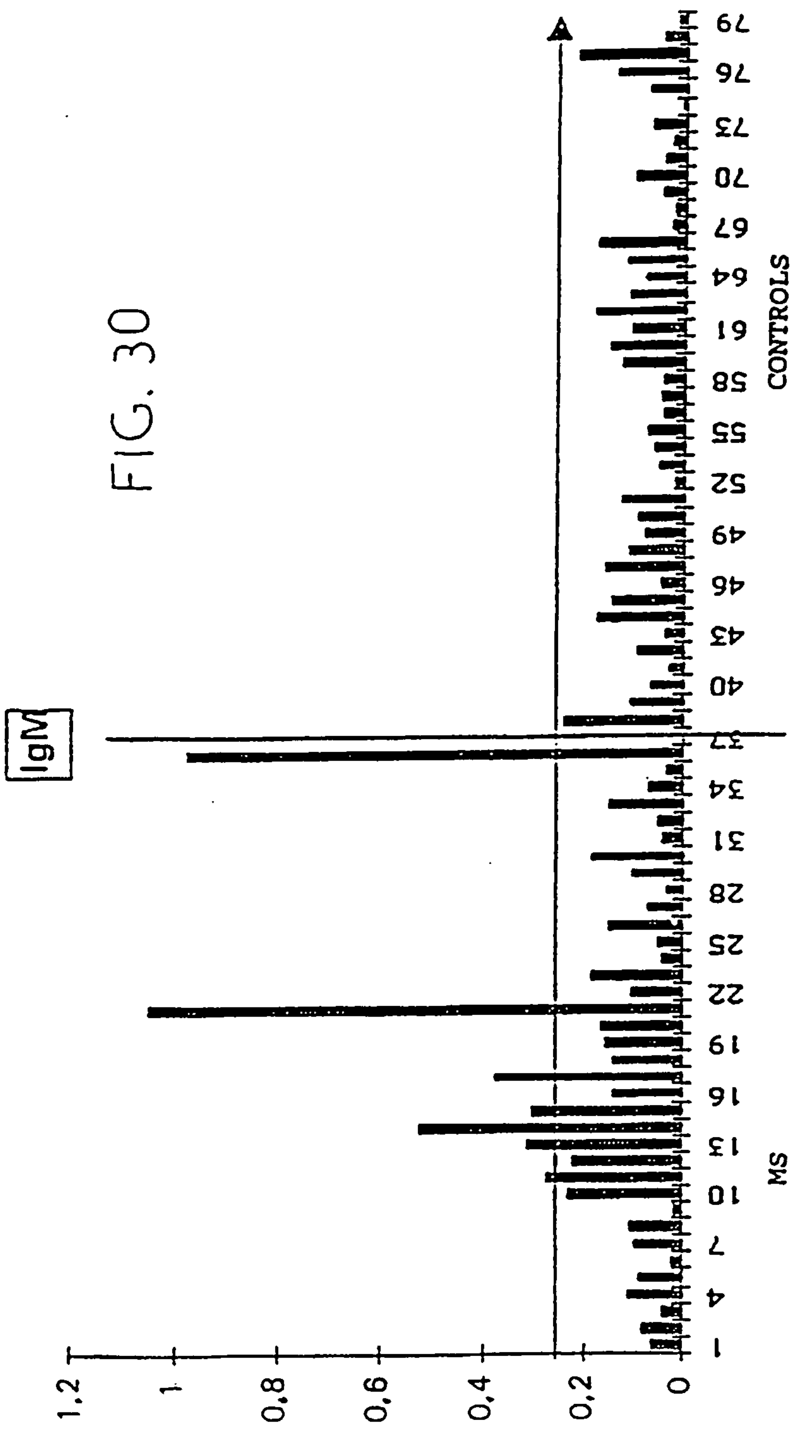
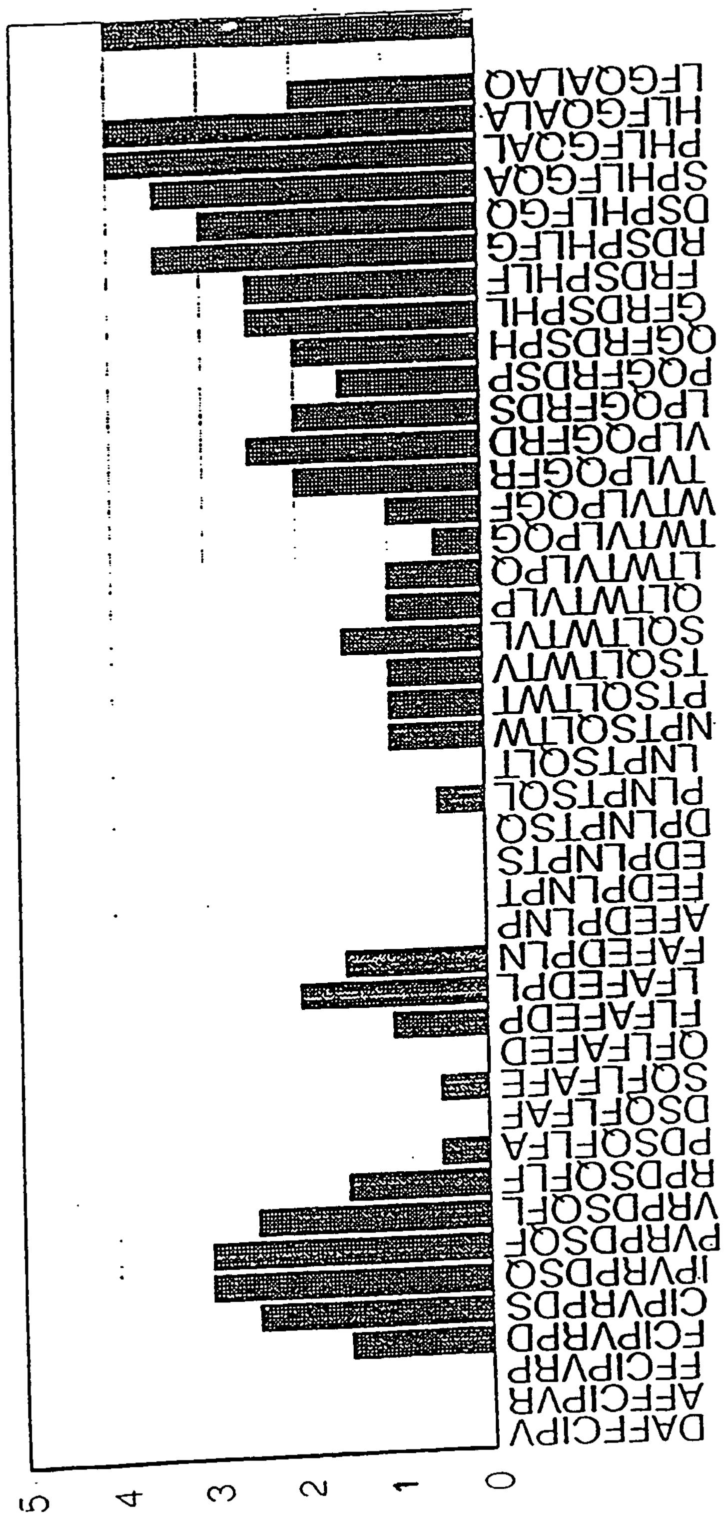

IgM
MS
CONTROLS
1
4
7
10
13
16
19
22
25
28
31
34
37
40
43
46
49
52
55
58
61
64
67
70
73
76
79
0
0,2
0,4
0,6
0,8
1
1,2

FIG. 30



0
1
2
3
4
5
DAFFCIPV
AFFCIPVR
FFCIPVRP
FCIPVRPD
CIPVRPDS
IPVRPDSQ
PVRPDSQF
VRPDSQFL
RPDSQFLF
PDSQFLFA
DSQFLFAF
SQFLFAFE
QFLFAFED
FLFAFEDP
LFAFEDPL
FAFEDPLN
AFEDPLNP
FEDPLNPT
EDPLNPTS
DPLNPTSQ
PLNPTSQL
LNPTSQLT
NPTSQLTW
PTSQLTWT
TSQLTWTV
SQLTWTVL
QLTWTVLP
LTWTVLPQ
TWTVLPQG
WTVLPQGF
TVLPQGFR
VLPQGFRD
LPQGFRDS
PQGFRDSP
QGFRDSPH
GFRDSPHL
FRDSPHLF
RDSPHLFG
DSPHLFGQ
SPHLFGQA
PHLFGQAL
HLFGQALA
LFGQALQ

FIG. 31

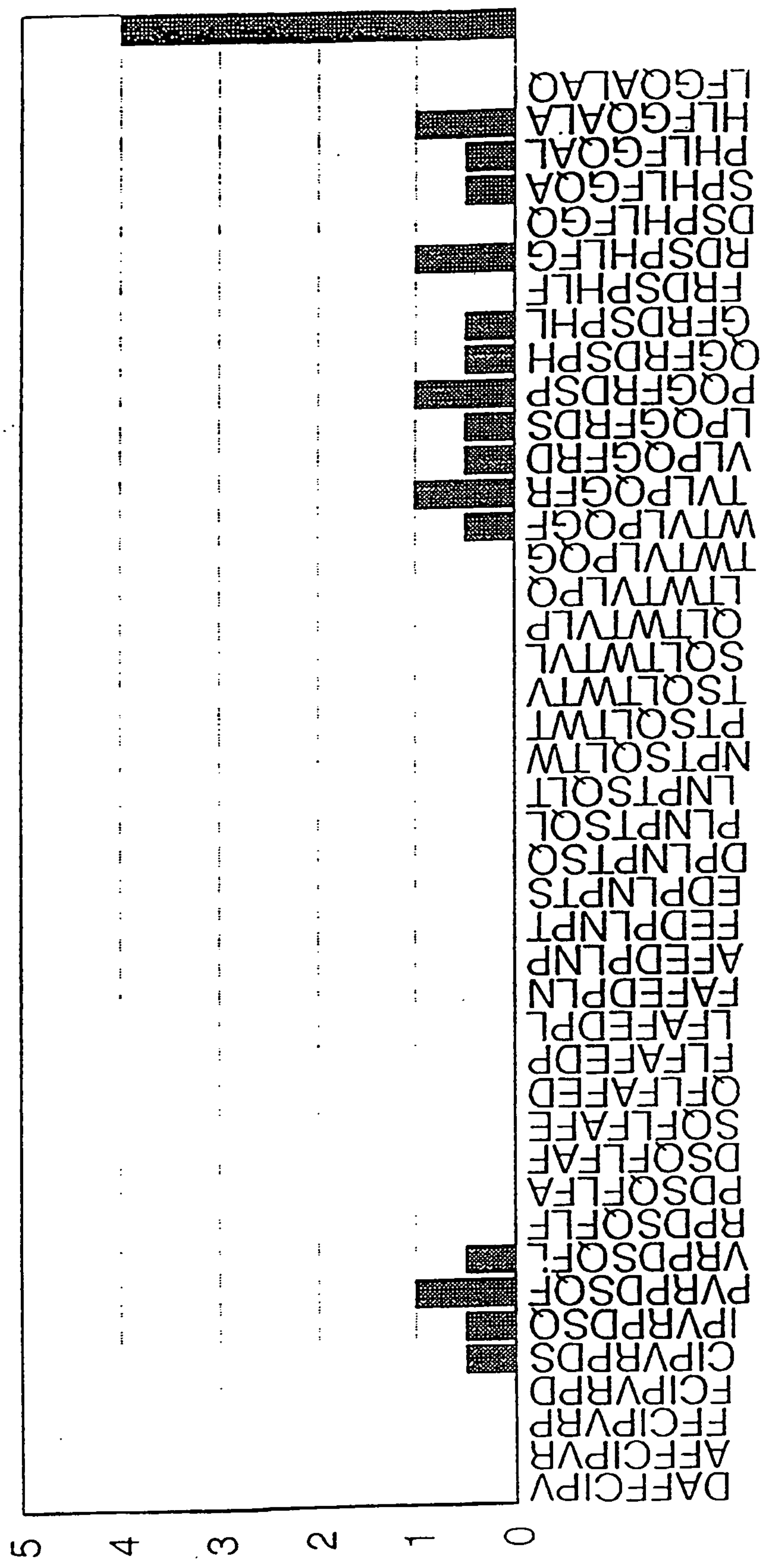

0
1
2
3
4
5
DAFFCIPV
AFFCIPVR
FFCIPVRP
FCIPVRPD
CIPVRPDS
IPVRPDSQ
PVRPDSQF
VRPDSQFL
RPDSQFLF
PDSQFLFA
DSQFLFAF
SQFLFAFE
QFLFAFED
FLFAFEDP
LFAFEDPL
FAFEDPLN
AFEDPLNP
FEDPLNPT
EDPLNPTS
DPLNPTSQ
PLNPTSQL
LNPTSQLT
NPTSQLTW
PTSQLTWT
TSQLTWTV
SQLTWTVL
QLTWTVLP
LTWTVLPQ
TWTVLPQG
WTVLPQGF
TVLPQGFR
VLPQGFRD
LPQGFRDS
PQGFRDSP
QGFRDSPH
GFRDSPHL
FRDSPHLF
RDSPHLFG
DSPHLFGQ
SPHLFGQA
PHLFGQAL
HLFGQAL
LFGQALQ

FIG. 32

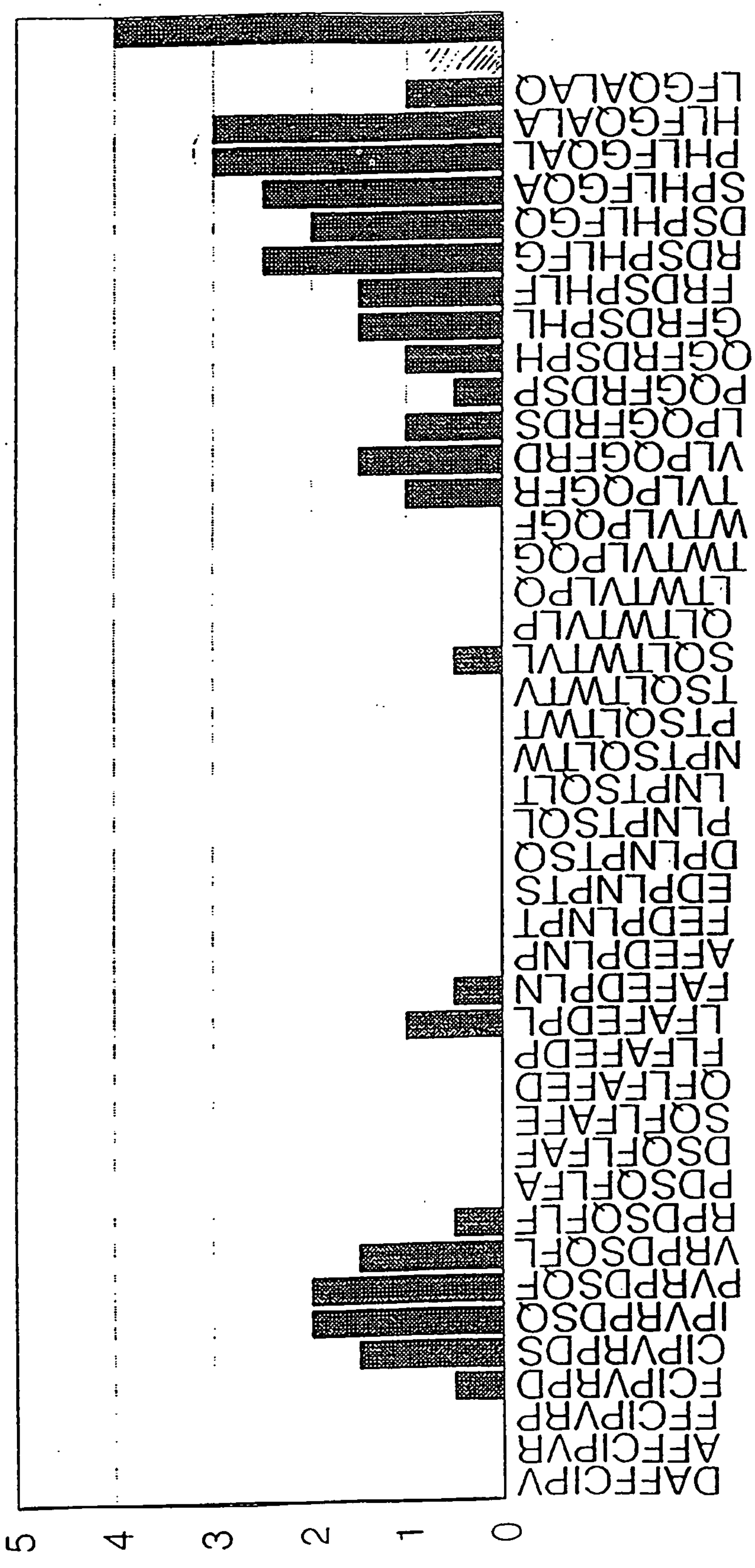

DAFFCIPV
AFFCIPVR
FFCIPVRP
FCIPVRPD
CIPVRPDS
IPVRPDSQ
PVRPDSQF
VRPDSQFL
RPDSQFLF
PDSQFLFA
DSQFLFAF
SQFLFAFE
QFLFAFED
FLFAFEDP
LFAFEDPL
FAFEDPLN
AFEDPLNP
FEDPLNPT
EDPLNPTS
DPLNPTSQ
PLNPTSQL
LNPTSQLT
NPTSQLTW
PTSQLTWT
TSQLTWTV
SQLTWTVL
QLTWTVLP
LTWTVLPQ
TWTVLPQG
WTVLPQGF
TVLPQGFR
VLPQGFRD
LPQGFRDS
PQGFRDSP
QGFRDSPH
GFRDSPHL
FRDSPHLF
RDSPHLFG
DSPHLFGQ
SPHLFGQA
PHLFGQAL
HLFGQALA
LFGQALQ
0
1
2
3
4
5

FIG. 33

FIG. 34

Cys-Ile-Pro-Val-Arg-Pro-Asp-Ser-Gln-Phe-Leu SEQ ID NO 41

Val-Leu-Pro-Gln-Gly-Phe-Arg-Asp-Ser-Pro-His-Leu-Phe-Gly-
Gln-Ala-Leu-Ala SEQ ID NO 42

Leu-Phe-Ala-Phe-Glu-Asp-Pro-Leu SEQ ID NO 43
Phe-Ala-Phe-Glu-Asp-Pro-Leu-Asn SEQ ID NO 44

FIG35


```
         10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
CTTCCCCAAC TAATAAGGAC CCCCCTTTCA ACCCAAACAG TCCAAAAGGA     50
L P Q L  I R T  P L S  T Q T V  Q K D
 F P N  . . G P  P F Q  P K Q  S K R T
  S P T  N K D  P P F N  P N S  P K G

CATAGACAAA GGAGTAAACA ATGAACCAAA GAGTGCCAAT ATTCCCTGGT    100
 I D K  G V N N  E P K  S A N  I P W L
  . T K  E . T  M N Q R  V P I  F P G
H R Q R  S K Q  . T K  E C Q Y  S L V

TATGCACCCT CCAAGCGGTG GGAGAAGAAT TCGGCCCAGC CAGAGTGCAT    150
  C T L  Q A V  G E E F  G P A  R V H
Y A P S  K R W  E K N  S A Q P  E C M
 M H P  P S G G  R R I  R P S  Q S A C

GTACCTTTTT CTCTCTCACA CTTGAAGCAA ATTAAAATAG ACNTAGGTNA    200
V P F S  L S H  L K Q  I K I D  X G X
 Y L F  L S H T  . S K  L K .  T . V N
  T F F  S L T  L E A N  . N R  X R X

ATTNTCAGAT AGCCCTGATG GYTATATTGA TGTTTTACAA GGATTAGGAC    250
 X S D  S P D G  Y I D  V L Q  G L G Q
  X Q I  A L M  X I L M  F Y K  D . D
I X R .  P . W  L Y .  C F T R  I R T

AATCCTTTGA TCTGACATGG AGAGATATAA TATTACTGCT AAATCAGACG    300
  S F D  L T W  R D I I  L L L  N Q T
N P L I  . H G  E I .  Y Y C .  I R R
 I L .  S D M E  R Y N  I T A  K S D A

CTAACCTCAA ATGAGAGAAG TGCTGCCATA ACTGGAGCCC GAGAGTTTGG    350
L T S N  E R S  A A I  T G A R  E F G
 . P Q  M R E V  L P .  L E P  E S L A
  N L K  . E K  C C H N  W S P  R V W

CAATCTCTGG TATCTCAGTC AGGTCAATGA TAGGATGACA ACGGAGGAAA    400
 N L W  Y L S Q  V N D  R M T  T E E R
  I S G  I S V  R S M I  G . Q  R R K
Q S L V  S Q S  G Q .  . D D N  G G K

GAGAACGATT CCCCACAGGG CAGCAGGCAG TTCCCAGTGT AGCTCCTCAT    450
  E R F  P T G  Q Q A V  P S V  A P H
E N D S  P Q G  S R Q  F P V .  L L I
 R T I  P H R A  A G S  S Q C  S S S L

TGGGACACAG AATCAGAACA TGGAGATTGG TGCCGCAGAC ATTTA         495
W D T E  S E H  G D W  C R R H  L
 G T Q  N Q N M  E I G  A A D  I
  G H R  I R T  W R L V  P Q T  F
```

FIG 36

```
         10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
CTTCCCCAAC TAATAAGGAC CCCCCTTTCA ACCCAAACAG TCCAAAAGGA     50
L  P  Q  L   I  R  T   P  L  S   T  Q  T  V   Q  K  D

CATAGACAAA GGAGTAAACA ATGAACCAAA GAGTGCCAAT ATTCCCTGGT    100
 I  D  K   G  V  N  N   E  P  K   S  A  N   I  P  W  L

TATGCACCCT CCAAGCGGTG GGAGAAGAAT TCGGCCCAGC CAGAGTGCAT    150
  C  T  L   Q  A  V   G  E  E  F   G  P  A   R  V  H

GTACCTTTTT CTCTCTCACA CTTGAAGCAA ATTAAAATAG ACCTAGGTAA    200
V  P  F  S   L  S  H   L  K  Q   I  K  I  D   L  G  K

ATTCTCAGAT AGCCCTGATG GYTATATTGA TGTTTTACAA GGATTAGGAC    250
  F  S  D   S  P  D  G   Y  I  D   V  L  Q   G  L  G  Q

AATCCTTTGA TCTGACATGG AGAGATATAA TATTACTGCT AAATCAGACG    300
  S  F  D   L  T  W   R  D  I  I   L  L  L   N  Q  T

CTAACCTCAA ATGAGAGAAG TGCTGCCATA ACTGGAGCCC GAGAGTTTGG    350
L  T  S  N   E  R  S   A  A  I   T  G  A  R   E  F  G

CAATCTCTGG TATCTCAGTC AGGTCAATGA TAGGATGACA ACGGAGGAAA    400
 N  L  W   Y  L  S  Q   V  N  D   R  M  T   T  E  E  R

GAGAACGATT CCCCACAGGG CAGCAGGCAG TTCCCAGTGT AGCTCCTCAT    450
  E  R  F   P  T  G   Q  Q  A  V   P  S  V   A  P  H

TGGGACACAG AATCAGAACA TGGAGATTGG TGCCGCAGAC ATTTACAACT    500
W  D  T  E   S  E  H   G  D  W   C  R  R  H   L  Q  L

TGCGTGCTAN AAGGACTNAG GAAAACTAGG AAGACTANGA ATTATTCAAN    550
 A  C  X   K  D  X  G   K  L  G   R  L  X   I  I  Q  X

GATGTCCACT ANNACACAGG GGAAAGGAAG AAAATCCTAC TGCCTTTCTG    600
  C  P  L   X  H  R   G  K  E  E   N  P  T   A  F  L

GAGAGACTAA GGGAGGCATT GAGGAAGCAT ACCAGGCAAG TGGACATTGG    650
E  R  L  R   E  A  L   R  K  H   T  R  Q  V   D  I  G

AGGCTCTGGA AAAGGGAAAA GTTGGGCAAA TTATATGCCT AATAGGGCTT    700
 G  S  G   K  G  K  S   W  A  N   Y  M  P   N  R  A  C

GCTTCCAGTG CAGTCTACAA GGACGCTTTA GAAAAGATTG TCCAAGTAGA    750
  F  Q  C   S  L  Q   G  R  F  R   K  D  C   P  S  R

AATAAGCCGC CCCTCGTCCA TGCCCCTTAT GTCAAGGGAA TCACTGGAAG    800
N  K  P  P   L  V  H   A  P  Y   V  K  G  I   T  G  R

GCCTACTGCC CCAGGGGACG AAGGTCCTCT GAGTCAGAAG CCACTAACCT    850
 P  T  A   P  G  D  E   G  P  L   S  Q  K   P  L  T  .

GA                                                        852
```

FIG 37

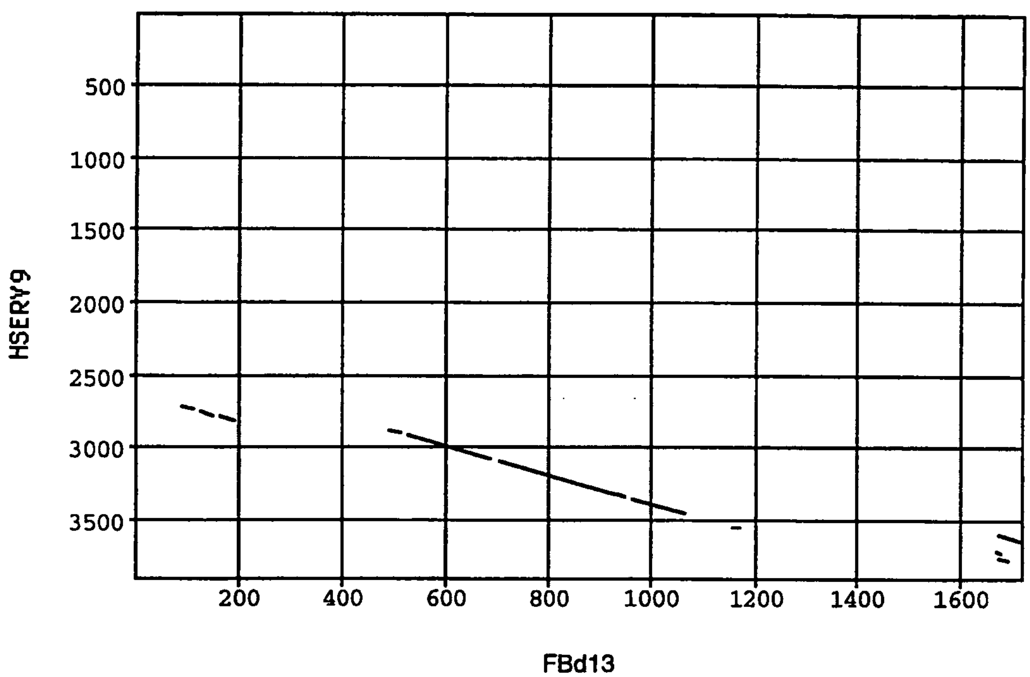

500
1000
1500
2000
2500
3000
3500
HSERY9
200
400
600
800
1000
1200
1400
1600
FBd13

FIG 38 a

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
AAGGAAACTC AGAAAGCCAA TACCCATTTA GTAAGATGGA CACCAGAAGC   50
K E T Q K A N T H L V R W T P E A
 R K L R K P I P I . . D G H Q K Q
  G N S E S Q Y P F S K M D T R S

AGAAGCAGCT TTCCAGGCCC TAAAGAAATC CCTAACCCAA GCCCCAGTGT   100
 E A A F Q A L K K S L T Q A P V L
  K Q L S R P . R N P . P K P Q C
R S S F P G P K E I P N P S P S V

TAAGCTTGCC AACGGGGCAA GACTTTTCTT TATATGTCAC AGAAAAACAG   150
  S L P T G Q D F S L Y V T E K Q
. A C Q R G K T F L Y M S Q K N R
 K L A N G A R L F F I C H R K T G

GAATAGCTCT AGGAGTCCTT ACACAGGTCC AAGGGACAAG CTTGCAACCT   200
E . L . E S L H R S K G Q A C N L
 N S S R S P Y T G P R D K L A T C
  I A L G V L T Q V Q G T S L Q P

GTGGCATACC TGAGTAAGGA AACTGATGTA NTGGCAAAGG GTTGGCCTCA   250
 W H T . V R K L M X W Q R V G L I
  G I P E . G N . C X G K G L A S
V A Y L S K E T D V X A K G W P H

TTGTTTACAG GTAGGGCAGC AGTAGCAGTC TTAGTTTCTG AAACAGTTAA   300
  V Y R . G S S S S L S F . N S .
L F T G R A A V A V L V S E T V K
 C L Q V G Q Q . Q S . F L K Q L K

AATAATACAG GGAAGAGATC TTACTGTGTG GACATCTCAT GATGTGAACG   350
N N T G K R S Y C V D I S . C E R
 I I Q G R D L T V W T S H D V N G
  . Y R E E I L L C G H L M M . T

GCATACTCAC TGCTAAAGAG GACTTGTGGC TGTCAGACAA CCATTTACTT   400
 H T H C . R G L V A V R Q P F T .
  I L T A K E D L W L S D N H L L
A Y S L L K R T C G C Q T T I Y L

AAATAGCAGG TTCTATTACT TGAAGTGCCA GTGCTGCGAC TGCACATTTG   450
  I A G S I T . S A S A A T A H L
K . Q V L L L E V P V L R L H I C
 N S R F Y Y L K C Q C C D C T F V

TGCAACTCTT AACCCAGCCA CATTTCTTCC AGACAATGAA GAAAAGATAG   500
C N S . P S H I S S R Q . R K D R
 A T L N P A T F L P D N E E K I E
  Q L L T Q P H F F Q T M K K R .
```

FIG38b

```
         10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
AACATAACTG TCAACAAGTA ATTGCTCAAA CCTATGCTGC TCGAGGGGAC    550
 T . L  S T S N  C S N  L C C  S R G P
  H N C  Q Q V  I A Q T  Y A A  R G D
N I T V  N K .  L L K  P M L L  E G T

CTTCTAGAGG TTCCCTTGAC TGATCCCGAC CTCAACTTGT ATACTGATGG    600
 S R G  S L D  . S R P  Q L V  Y . W
L L E V  P L T  D P D  L N L Y  T D G
 F . R  F P . L  I P T  S T C  I L M E

AAGTTCCTTG GCAGAAAAAG GACTTTGAAA AGCGGGGTAT GCAGTGATCA    650
K F L G  R K R  T L K  S G V C  S D Q
 S S L  A E K G  L . K  A G Y  A V I S
 V P W  Q K K  D F E K  R G M  Q . S

GTGATAATGG AATACTTGAA AGTAATCGCC TCACTCCAGG AACTAGTGCT    700
 . . W  N T . K  . S P  H S R  N . C S
 D N G  I L E  S N R L  T P G  T S A
V I M E  Y L K  V I A  S L Q E  L V L

CACCTGGCAG AACTAATAGC CCTCACTTGG GCACTAGAAT TAGGAGAAGG    750
 P G R  T N S  P H L G  T R I  R R R
H L A E  L I A  L T W  A L E L  G E G
 T W Q  N . . P  S L G  H . N  . E K E

AAAAAGGGTA AATATATATT CAGACTCTAA GTATGCTTAC CTAGTCCTCC    800
K K G K  Y I F  R L .  V C L P  S P P
 K R V  N I Y S  D S K  Y A Y  L V L H
 K G .  I Y I  Q T L S  M L T  . S S

ATGCCCATGC AGCAATATGG AGAGAGAGGG AATTCCTAAC TTCTGAGGGA    850
 C P C  S N M E  R E G  I P N  F . G N
 A H A  A I W  R E R E  F L T  S E G
M P M Q  Q Y G  E R G  N S . L  L R E

ACACCTATCA ACCATCAGGG AAGCCATTAG GAGATTATTA TTGGCTGTAC    900
 T Y Q  P S G  K P L G  D Y Y  W L Y
T P I N  H Q G  S H .  E I I I  G C T
 H L S  T I R E  A I R  R L L  L A V Q

AGAAACCTAA AGAGGTGGCA GTCTTACACT GCCAGGGTCA TCAGGAAGAA    950
R N L K  R W Q  S Y T  A R V I  R K K
 E T .  R G G S  L T L  P G S  S G R R
 K P K  E V A  V L H C  Q G H  Q E E

GAGGAAAGGG AAATAGAAGG CAATCGCCAA GCGGATATTG AAGCAAAAAA   1000
 R K G  K . K A  I A K  R I L  K Q K K
 G K G  N R R  Q S P S  G Y .  S K K
E E R E  I E G  N R Q  A D I E  A K K
```

FIG 38 C

```
         10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
AGCCGCAAGG CAGGACTCTC CATTAGAAAT GCTTATAGAA GGACCCCTAG   1050
 P  Q  G   R  T  L   H  .  K  C   L  .  K   D  P  .
S  R  K  A   G  L  S   I  R  N   A  Y  R  R   T  P  S
 A  A  R   Q  D  S  P   L  E  M   L  I  E   G  P  L  V

TATGGGGTAA TCCCCTCTGG GAAACCAAGC CCCAGTACTC AGCAGGAAAA   1100
Y  G  V  I   P  S  G   K  P  S   P  S  T  Q   Q  E  K
 M  G  .   S  P  L  G   N  Q  A   P  V  L   S  R  K  N
  W  G  N   P  L  W   E  T  K  P   Q  Y  S   A  G  K

ATAGAATAGG AAACCTCACA AGGACATACT TTCCTCCCCT CCAGATGGCT   1150
 .  N  R   K  P  H  K   D  I  L   S  S  P   P  D  G  .
 R  I  G   N  L  T   R  T  Y  F   P  P  L   Q  M  A
I  E  .  E   T  S  Q   G  H  T   F  L  P  S   R  W  L

AGCCACTGAG GAAGGAA                                       1167
  P  L  R   K  E
S  H  .  G   R
 A  T  E   E  G
```

```
         10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
AACTTGCGTG CTAGAAGGAC TAAGGAAAAC TAGGAAGACT ATGAATTATT    50
N  L  R  A   R  R  T   K  E  N   .  E  D  Y   E  L  F
 T  C  V   L  E  G  L   R  K  T   R  K  T   M  N  Y  S
  L  A  C   .  K  D   .  G  K  L   G  R  L   .  I  I
```

FIG 39
a

```
CAATGATGTC CACTATAACA CAGGGGAAAG GAAGAAAATC CTACTGCCTT   100
 N  D  V   H  Y  N  T   G  E  R   K  K  I   L  L  P  F
  M  M  S   T  I  T   Q  G  K  G   R  K  S   Y  C  L
Q  .  C  P   L  .  H   R  G  K   E  E  N  P   T  A  F

TCTGGAGAGA CTAAGGGAGG CATTGAGGAA GCATACCAGG CAAGTGGACA   150
  W  R  D   .  G  R   H  .  G  S   I  P  G   K  W  T
S  G  E  T   K  G  G   I  E  E   A  Y  Q  A   S  G  H
 L  E  R   L  R  E  A   L  R  K   H  T  R   Q  V  D  I

TTGGAGGCTC TGGAAAAGGG AAAAGTTGGG CAAATTGAAT GCCTAATAGG   200
L  E  A  L   E  K  G   K  V  G   Q  I  E  C   L  I  G
 W  R  L   W  K  R  E   K  L  G   K  L  N   A  .  .  G
  G  G  S   G  K  G   K  S  W  A   N  .  M   P  N  R

GCTTGCTTCC AGTGCAGTCT ACAAGGACGC TTTAGAAAAG ATTGTCCAAG   250
 L  A  S   S  A  V  Y   K  D  A   L  E  K   I  V  Q  V
  L  L  P   V  Q  S   T  R  T  L   .  K  R   L  S  K
A  C  F  Q   C  S  L   Q  G  R   F  R  K  D   C  P  S

TAGAAATAAG CCGCCCCTCG TCCATGCCCC TTATGTCAAG GGAATCACTG   300
  E  I  S   R  P  S   S  M  P  L   M  S  R   E  S  L
.  K  .  A   A  P  R   P  C  P   L  C  Q  G   N  H  W
 R  N  K   P  P  L  V   H  A  P   Y  V  K   G  I  T  G

GAAGGCCTAC TGCCCCAGGG GACGAAGGTC CTCTGAGTCA GAAGCCACTA   350
E  G  L  L   P  Q  G   T  K  V   L  .  V  R   S  H  .
 K  A  Y   C  P  R  G   R  R  S   S  E  S   E  A  T  N
  R  P  T   A  P  G   D  E  G  P   L  S  Q   K  P  L

ACCTGATGAT CCAGCAGCAG GACTGAGGGT GCCCGGGGCA AGTGCCAGCC   400
 P  D  D   P  A  A  G   L  R  V   P  G  A   S  A  S  P
  L  M  I   Q  Q  Q   D  .  G  C   P  G  Q   V  P  A
T  .  .  S   S  S  R   T  E  G   A  R  G  K   C  Q  P

CATGCCATCA CCCTCAGAGC CCCGGGTATG TTTGACCATT GAGAGCCAGG   450
  C  H  H   P  Q  S   P  G  Y  V   .  P  L   R  A  R
H  A  I  T   L  R  A   P  G  M   F  D  H  .   E  P  G
 M  P  S   P  S  E  P   R  V  C   L  T  I   E  S  Q  E

AAGTTAACTG TCTCCTGGAC ACTGGCGCAG CCTTCTCAGT CTTACTTTCC   500
K  L  T  V   S  W  T   L  A  Q   P  S  Q  S   Y  F  P
 S  .  L   S  P  G  H   W  R  S   L  L  S   L  T  F  L
  V  N  C   L  L  D   T  G  A  A   F  S  V   L  L  S
```

FIG 39b

```
         10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
TGTCCCAGAC AATTGTCCTC CAGATCTGTC ACTATCCGAG GGGTCCTAAG   550
 V  P  D   N  C  P  P   D  L  S   L  S  E   G  S  .  D
  S  Q  T   I  V  L   Q  I  C  H   Y  P  R   G  P  K
C  P  R  Q   L  S  S   R  S  V   T  I  R  G   V  L  R

ACAGCCAGTC ACTACATACT TCTCTCAGCC ACTAAGTTGT GACTGGGGAA   600
  S  Q  S   L  H  T   S  L  S  H   .  V  V   T  G  E
T  A  S  H   Y  I  L   L  S  A   T  K  L  .   L  G  N
 Q  P  V   T  T  Y  F   S  Q  P   L  S  C   D  W  G  T

CTTTACTCTT TTCACATGCT TTTCTAATTA TGCCTGAAAG CCCCACTCCC   650
L  Y  S  F   H  M  L   F  .  L   C  L  K  A   P  L  P
 F  T  L   F  T  C  F   S  N  Y   A  .  K   P  H  S  L
  L  L  F   S  H  A   F  L  I  M   P  E  S   P  T  P

TTGTTAGGGA GAGACATTTT AGCAAAAGCA GGGGCCATTA TACACCTGAA   700
 C  .  G   E  T  F  .   Q  K  Q   G  P  L   Y  T  .  T
  V  R  E   R  H  F   S  K  S  R   G  H  Y   T  P  E
L  L  G  R   D  I  L   A  K  A   G  A  I  I   H  L  N

CATAGGAAAA GGAATACCCA TTTGCTGTCC CCTGCTTGAG GAAGGAATTA   750
  .  E  K   E  Y  P   F  A  V  P   C  L  R   K  E  L
H  R  K  R   N  T  H   L  L  S   P  A  .  G   R  N  .
 I  G  K   G  I  P  I   C  C  P   L  L  E  E  G  I  N

ATCCTGAAGT CTGGGCAATA GAAGGACAAT ATGGACAAGC AAAGAATGCC   800
I  L  K  S   G  Q  .   K  D  N   M  D  K  Q   R  M  P
 S  .  S   L  G  N  R   R  T  I   W  T  S   K  E  C  P
  P  E  V   W  A  I   E  G  Q  Y   G  Q  A   K  N  A

CGTCCTGTTC AAGTTAAACT AAAGGATTCT GCCTCCTTTC CCTACCAAAG   850
 V  L  F   K  L  N  .   R  I  L   P  P  F   P  T  K  G
  S  C  S   S  .  T   K  G  F  C   L  L  S   L  P  K
R  P  V  Q   V  K  L   K  D  S   A  S  F  P   Y  Q  R

GAAGTACCCT CTTAGACCCG AGGCCCTACA AGGACTCAAA AGATTGTTAA   900
  S  T  L   L  D  P   R  P  Y  K   D  S  K   D  C  .
E  V  P  S   .  T  R   G  P  T   R  T  Q  K   I  V  K
 K  Y  P   L  R  P  E   A  L  Q   G  L  K   R  L  L  R

GGACCTAAAA GCCCAAGGCC TAGTAAAACC ATGCAGTAGC CCCTGCAATA   950
G  P  K  S   P  R  P   S  K  T   M  Q  .  P   L  Q  Y
 D  L  K   A  Q  G  L   V  K  P   C  S  S   P  C  N  T
  T  .  K   P  K  A   .  .  N  H   A  V  A   P  A  I

CTCCAATTTT AGGAGTAAGG AAACCCAACG GACAGTGGAG GTTAGTGCAA  1000
 S  N  F   R  S  K  E   T  Q  R   T  V  E   V  S  A  R
  P  I  L   G  V  R   K  P  N  G   Q  W  R   L  V  Q
L  Q  F  .   E  .  G   N  P  T   D  S  G  G   .  C  K
```

FIG 39 C

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
GATCTCAGGA TTATTAATGA GGCTGTTTTT CCTCTATACC CAGCTGTATC    1050
 S  Q  D  Y  .  .  G  C  F  S  S  I  P  S  C  I
D  L  R  I  I  N  E  A  V  F  P  L  Y  P  A  V  S
 I  S  G  L  L  M  R  L  F  F  L  Y  T  Q  L  Y  L

TAGCCCTTAT ACTCTGCTTT CCCTAATACC AGAGGAAGCA GAGTAGTTTA    1100
.  P  L  Y  S  A  F  P  N  T  R  G  S  R  V  V  Y
 S  P  Y  T  L  L  S  L  I  P  E  E  A  E  .  F  T
  A  L  I  L  C  F  P  .  Y  Q  R  K  Q  S  S  L

CAGTCCTGGA CCTTAAGGAT GCCTCTTTCT GCATCCCTGT ACATCCTGAT    1150
 S  P  G  P  .  G  C  L  F  L  H  P  C  T  S  .  F
  V  L  D  L  K  D  A  S  F  C  I  P  V  H  P  D
Q  S  W  T  L  R  M  P  L  S  A  S  L  Y  I  L  I

TCTCAATTCT TGTTTGTCTT TGAAGATCCT TTGAACCCAA TGTCTCAATT    1200
  S  I  L  V  C  L  .  R  S  F  E  P  N  V  S  I
S  Q  F  L  F  V  F  E  D  P  L  N  P  M  S  Q  F
 L  N  S  C  L  S  L  K  I  L  .  T  Q  C  L  N  S

CACCTGGACT GTTTTACCCC AGGGGTTCCG GGATAGCCCC CATCTATTTG    1250
H  L  D  C  F  T  P  G  V  P  G  .  P  P  S  I  W
 T  W  T  V  L  P  Q  G  F  R  D  S  P  H  L  F  G
  P  G  L  F  Y  P  R  G  S  G  I  A  P  I  Y  L

GCCAGGCATT AGCCCAAGAC TTGAGCCAAT TCTCATACCT GGACATCTTG    1300
 P  G  I  S  P  R  L  E  P  I  L  I  P  G  H  L  V
  Q  A  L  A  Q  D  L  S  Q  F  S  Y  L  D  I  L
A  R  H  .  P  K  T  .  A  N  S  H  T  W  T  S  C

TCCTTCGGTA TGGGATGATT TAATTTTAGC CACCCGTTCA GAAACCTTGT    1350
  L  R  Y  G  M  I  .  F  .  P  P  V  Q  K  P  C
S  F  G  M  G  .  F  N  F  S  H  P  F  R  N  L  V
 P  S  V  W  D  D  L  I  L  A  T  R  S  E  T  L  C

GCCATCAAGC CACCCAAGCG TTCTTAAATT TCCTCACTCC GTGTGGCTAC    1400
A  I  K  P  P  K  R  S  .  I  S  S  L  R  V  A  T
 P  S  S  H  P  S  V  L  K  F  P  H  S  V  W  L  Q
  H  Q  A  T  Q  A  F  L  N  F  L  T  P  C  G  Y

AAGGTTTCCA AACCAAAGGC TCAGCTCTGC TCACAGCAGG TTAAATACTT    1450
 R  F  P  N  Q  R  L  S  S  A  H  S  R  L  N  T  .
  G  F  Q  T  K  G  S  A  L  L  T  A  G  .  I  L
K  V  S  K  P  K  A  Q  L  C  S  Q  Q  V  K  Y  L

AGGGTTAAAA TTATCCAAAG GCACCAGGGC CCTCTGTGAG GAATGTATCC    1500
  G  .  N  Y  P  K  A  P  G  P  S  V  R  N  V  S
R  V  K  I  I  Q  R  H  Q  G  P  L  .  G  M  Y  P
 G  L  K  L  S  K  G  T  R  A  L  C  E  E  C  I  Q
```

FIG 39
d

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
AACCTGTACT GGCTTATCTT CATCCCAAAA CCCTAAAGCA ACTAAGAAGG   1550
N L Y W  L I F  I P K  P . S N  . E G
 T C T  G L S S  S Q N  P K A  T K K V
  P V L  A Y L  H P K T  L K Q  L R R

TCCTTGGCAT AACAGGTTTC TGCCGAA                            1577
 P W H  N R F L  P
  L G I  T G F  C R
S L A .  Q V S  A E
```

FIG 40

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
TCCAGCAGCA GGACTGAGGG TGCCCGGGGC AAGTGCCAGC CCATGCCATC     50
S  S  S  R   T  E  G   A  R  G   K  C  Q  P   M  P  S

ACCCTCAGAG CCCCGGGTAT GTTTGACCAT TGAGAGCCAG GAAGTTAACT    100
 P  S  E   P  R  V  C   L  T  I   E  S  Q   E  V  N  C

GTCTCCTGGA CACTGGCGCA GCCTTCTCAG TCTTACTTTC CTGTCCCAGA    150
 L  L  D   T  G  A   A  F  S  V   L  L  S   C  P  R

CAATTGTCCT CCAGATCTGT CACTATCCGA GGGGTCCTAA GACAGCCAGT    200
Q  L  S  S   R  S  V   T  I  R   G  V  L  R   Q  P  V

CACTACATAC TTCTCTCAGC CACTAAGTTG TGACTGGGGA ACTTTACTCT    250
 T  T  Y   F  S  Q  P   L  S  C   D  W  G   T  L  L  F

TTTCACATGC TTTTCTAATT ATGCCTGAAA GCCCCACTCC CTTGTTAGGG    300
 S  H  A   F  L  I   M  P  E  S   P  T  P   L  L  G

AGAGACATTT TAGCAAAAGC AGGGGCCATT ATACACCTGA ACATAGGAAA    350
R  D  I  L   A  K  A   G  A  I   I  H  L  N   I  G  K

AGGAATACCC ATTTGCTGTC CCCTGCTTGA GGAAGGAATT AATCCTGAAG    400
 G  I  P   I  C  C  P   L  L  E   E  G  I   N  P  E  V

TCTGGGCAAT AGAAGGACAA TATGGACAAG CAAAGAATGC CCGTCCTGTT    450
 W  A  I   E  G  Q   Y  G  Q  A   K  N  A   R  P  V

CAAGTTAAAC TAAAGGATTC TGCCTCCTTT CCCTACCAAA GGAAGTACCC    500
Q  V  K  L   K  D  S   A  S  F   P  Y  Q  R   K  Y  P

TCTTAGACCC GAGGCCCTAC AAGGACTCAA AAGATTGTTA AGGACCT       547
 L  R  P   E  A  L  Q   G  L  K   R  L  L   R  T
```

FIG 41

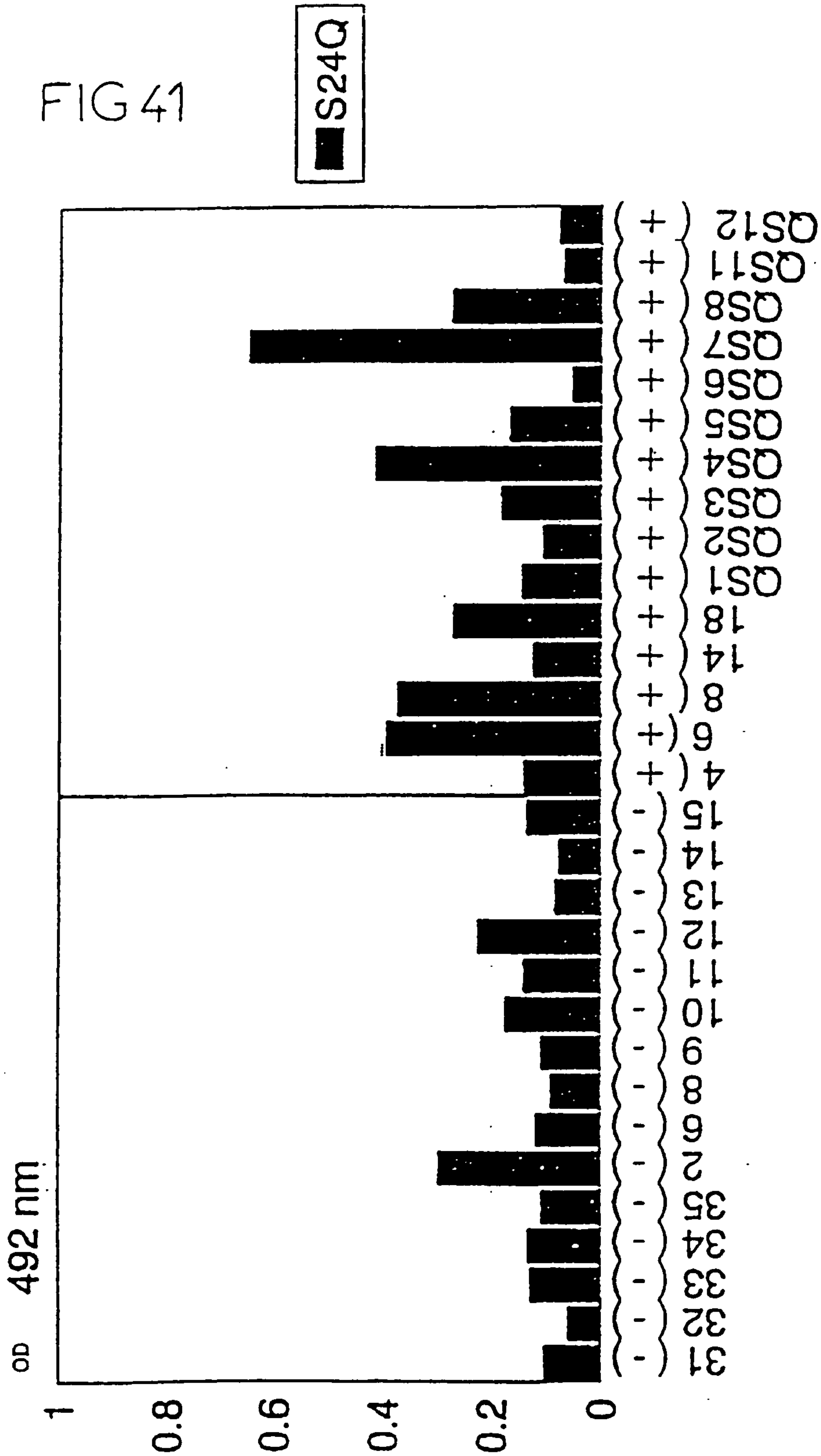
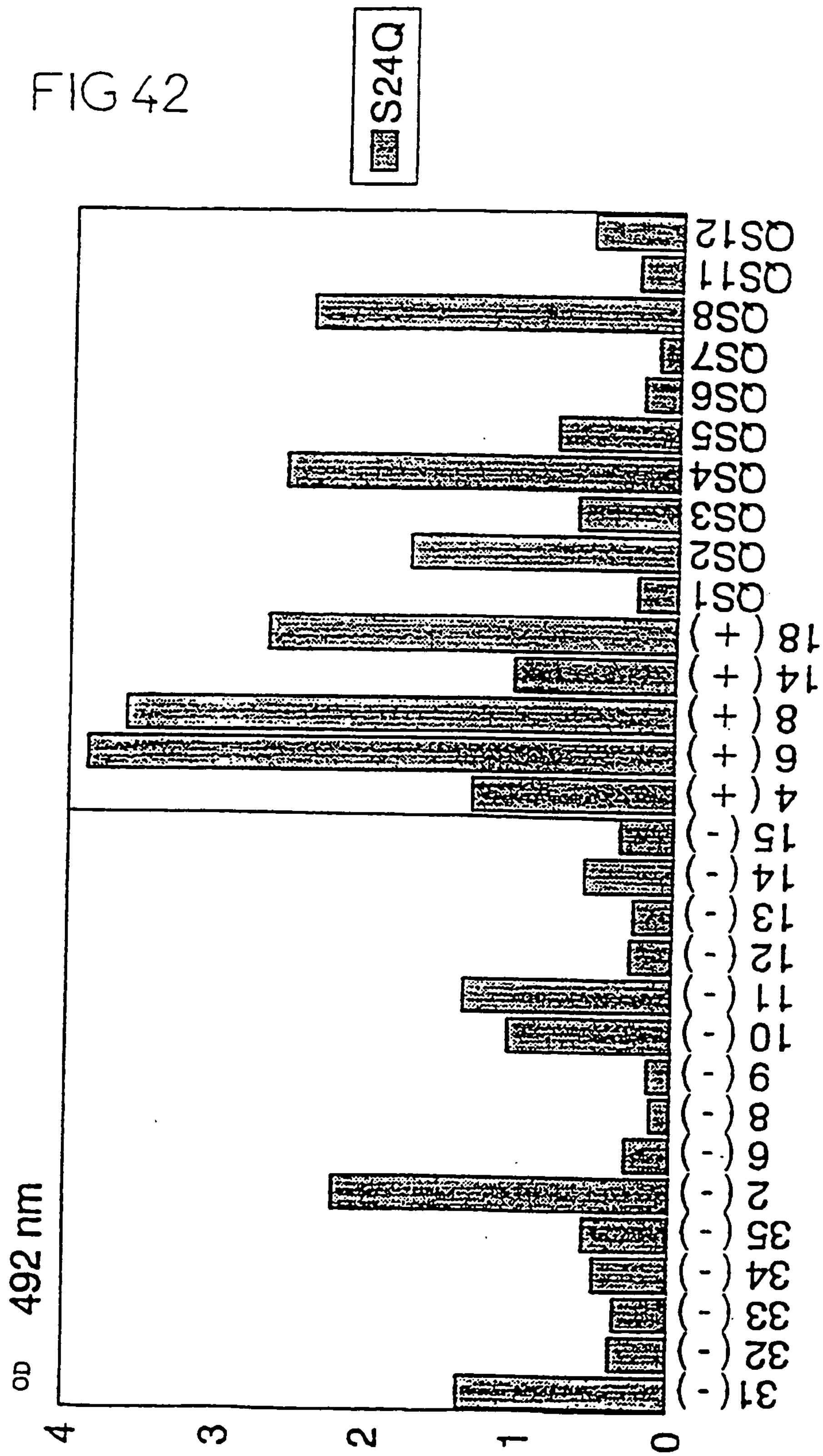

S24Q
OD 492 nm
0
0.2
0.4
0.6
0.8
1
31 (-)
32 (-)
33 (-)
34 (-)
35 (-)
2 (-)
6 (-)
8 (-)
9 (-)
10 (-)
11 (-)
12 (-)
13 (-)
14 (-)
15 (-)
4 (+)
6 (+)
8 (+)
14 (+)
18 (+)
QS1 (+)
QS2 (+)
QS3 (+)
QS4 (+)
QS5 (+)
QS6 (+)
QS7 (+)
QS8 (+)
QS11 (+)
QS12 (+)

FIG 42


S24Q
OD 492 nm
0
1
2
3
4
31 (-)
32 (-)
33 (-)
34 (-)
35 (-)
2 (-)
6 (-)
8 (-)
9 (-)
10 (-)
11 (-)
12 (-)
13 (-)
14 (-)
15 (-)
4 (+)
6 (+)
8 (+)
14 (+)
18 (+)
QS1
QS2
QS3
QS4
QS5
QS6
QS7
QS8
QS11
QS12

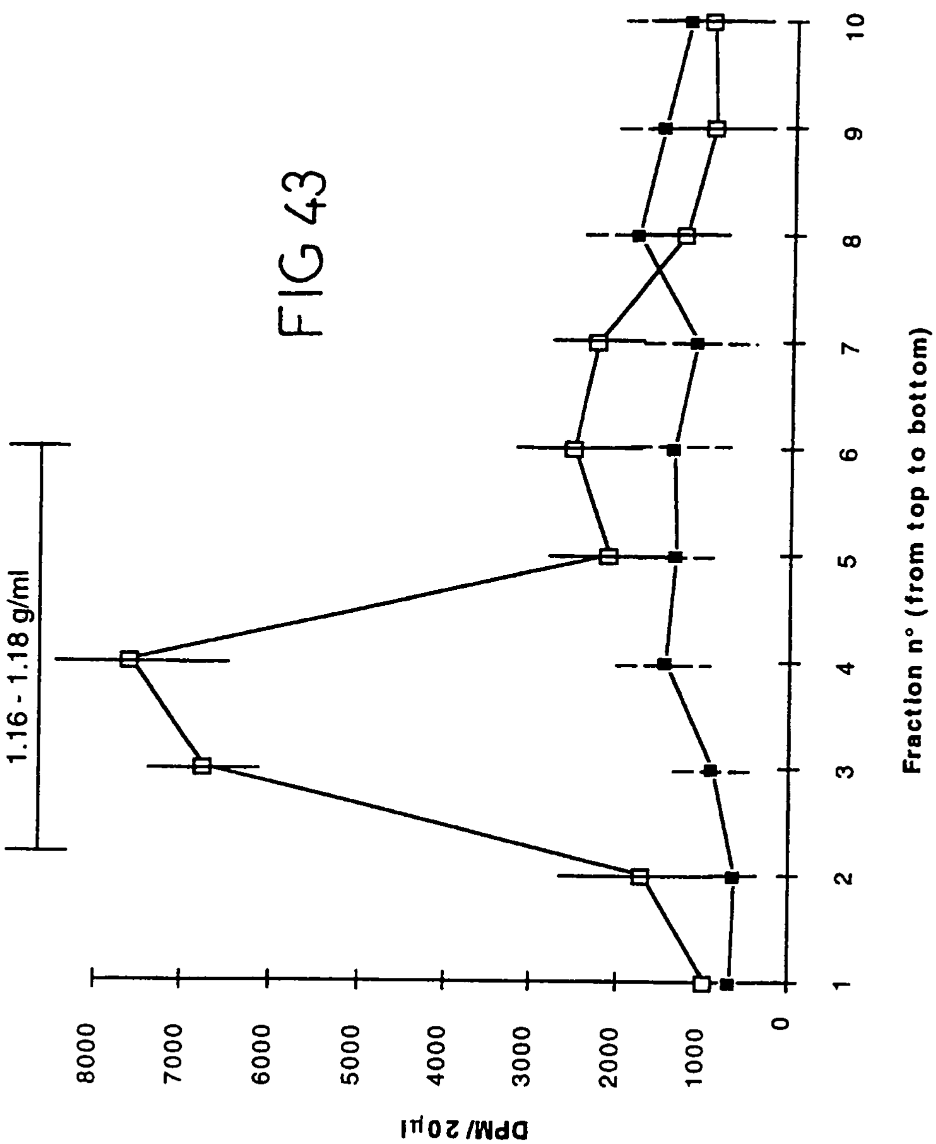

1.16 - 1.18 g/ml
DPM/ 20µl
8000
7000
6000
5000
4000
3000
2000
1000
0
1
2
3
4
5
6
7
8
9
10
Fraction n° (from top to bottom)

FIG 43

FIG 44

```
                                   c g  a
PAN-UO     5'-⊥tggaaagtgttacccc-3'
PAN-UI      5'-⊥agtgttaccccaagg-3'
                   c g  a  g

                                                                                                                              c     g g
PAN-DI                                                                                                                   3'-atgtacctactgtacgac⌉-5'

HTLV-1     tggaaagtactaccccaagg   gtttaaaaatagtcccaccctgttcgaaatgcagctggcccatatcctgcagcccattcggcaagctttcccccaatgcactattcttcag   tacatggatgacattctc
            W  K  V  L  P  Q  G     F  K  N  S  P  T  L  F  E  M  Q  L  A  H  I  L  Q  P  I  R  Q  A  F  P  Q  C  T  I  L  Q     Y  M  D  D  I  L

HIV-1      tacaatgtgcttccacaggg   atggaaaggatcaccagcaatattccaaagtagcatgacaaaaatcttagagccttttaaaaaacaaaatccagacatagttatctatcaa   tacatggatgatttgtat
            Y  N  V  L  P  Q  G     W  K  G  S  P  A  I  F  Q  S  S  M  T  K  I  L  E  P  F  K  K  Q  N  P  D  I  V  I  Y  Q     Y  M  D  D  L  Y

MoMLV      tggaccagactcccacaggg   tttcaaaaacagtcccaccctgtttgatgaggcactgcacagagacctagcagacttccggatccagcacccagacttgatcctgctacag   tacgtggatgacttactg
            W  T  R  L  P  Q  G     F  K  N  S  P  T  L  F  D  E  A  L  H  R  D  L  A  D  F  R  I  Q  H  P  D  L  I  L  L  Q     Y  V  D  D  L  L

MPMV       tggaaggttttaccacaagg   tatggccaacagtcctaccttatgtcaaaaatatgtggccacagccatacataaggttagacatgcctggaaacaaatgtatattatacat   tacatggatgacatccta
            W  K  V  L  P  Q  G     M  A  N  S  P  T  L  C  Q  K  Y  V  A  T  A  I  H  K  V  R  H  A  W  K  Q  M  Y  I  I  H     Y  M  D  D  I  L

ERV9       tggatggtcttgccccaagg   gtttagggatagccctcatctgtttggtcaggccctagccaaagatctaggccacttctcaagtccaggc------actctggtccttcaa   tatgtggatgatttactt
            W  M  V  L  P  Q  G     F  R  D  S  P  H  L  F  G  Q  A  L  A  K  D  L  G  H  F  S  S  P  G  -  -  T  L  V  L  Q     Y  V  D  D  L  L

MSRV-cpol                         gttcagggatagcccccatctatttggccaggcattagcccaagacttgagccaattctcatacctggac------actcttgtccttcag
                                    F  R  D  S  P  H  L  F  G  Q  A  L  A  Q  D  L  S  Q  F  S  Y  L  D  -  -  T  L  V  L  Q
                                       K                                      Y                                      R
                                                                                                                     W

DpV1                                   Perox-5'-catctitttggicaggcaitagc-3'

CpV1B                                                        5'-cttgagccagttctcatacctgga-3'
```

FIG 45

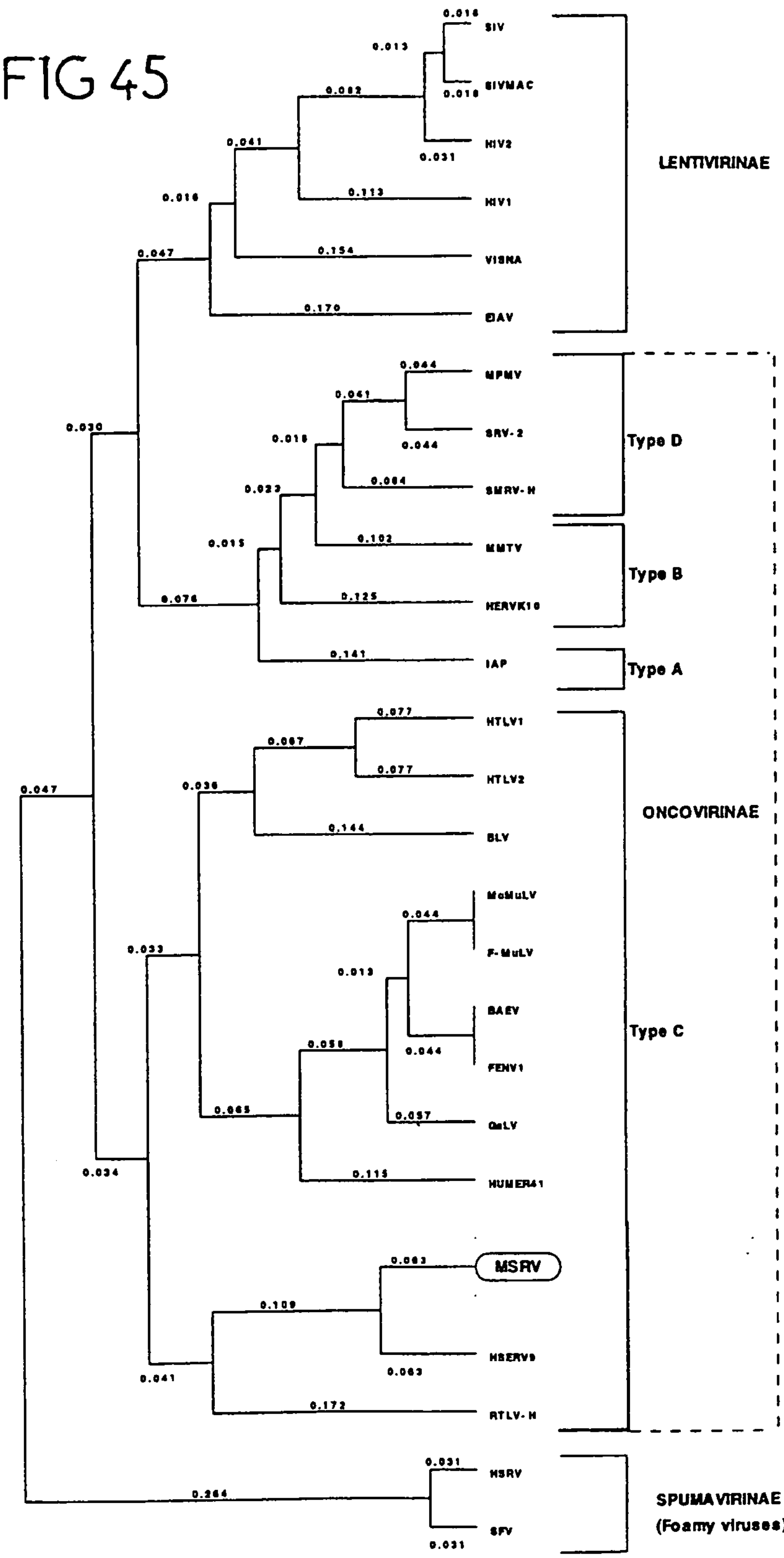

SIV
SIVMAC
HIV2
HIV1
VISNA
EIAV
LENTIVIRINAE
MPMV
SRV-2
SMRV-H
Type D
MMTV
HERVK10
Type B
IAP
Type A
HTLV1
HTLV2
BLV
ONCOVIRINAE
MoMuLV
F-MuLV
BAEV
FENV1
GaLV
HUMER41
Type C
MSRV
HSERV9
RTLV-H
HSRV
SFV
SPUMAVIRINAE
(Foamy viruses)

FIG 46

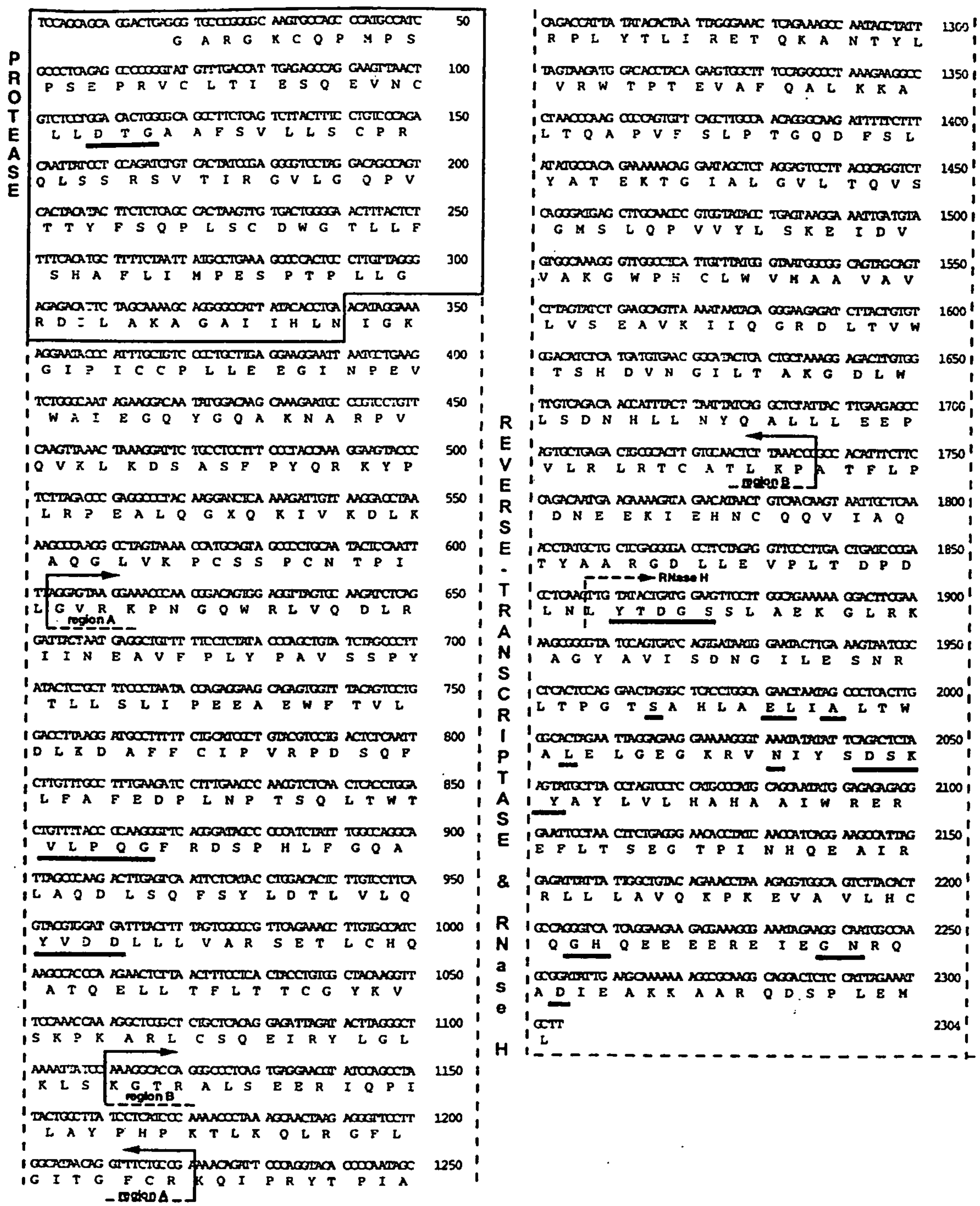

PROTEASE
REVERSE-TRANSCRIPTASE & RNase H
region A
region B
RNase H

FIG 47A

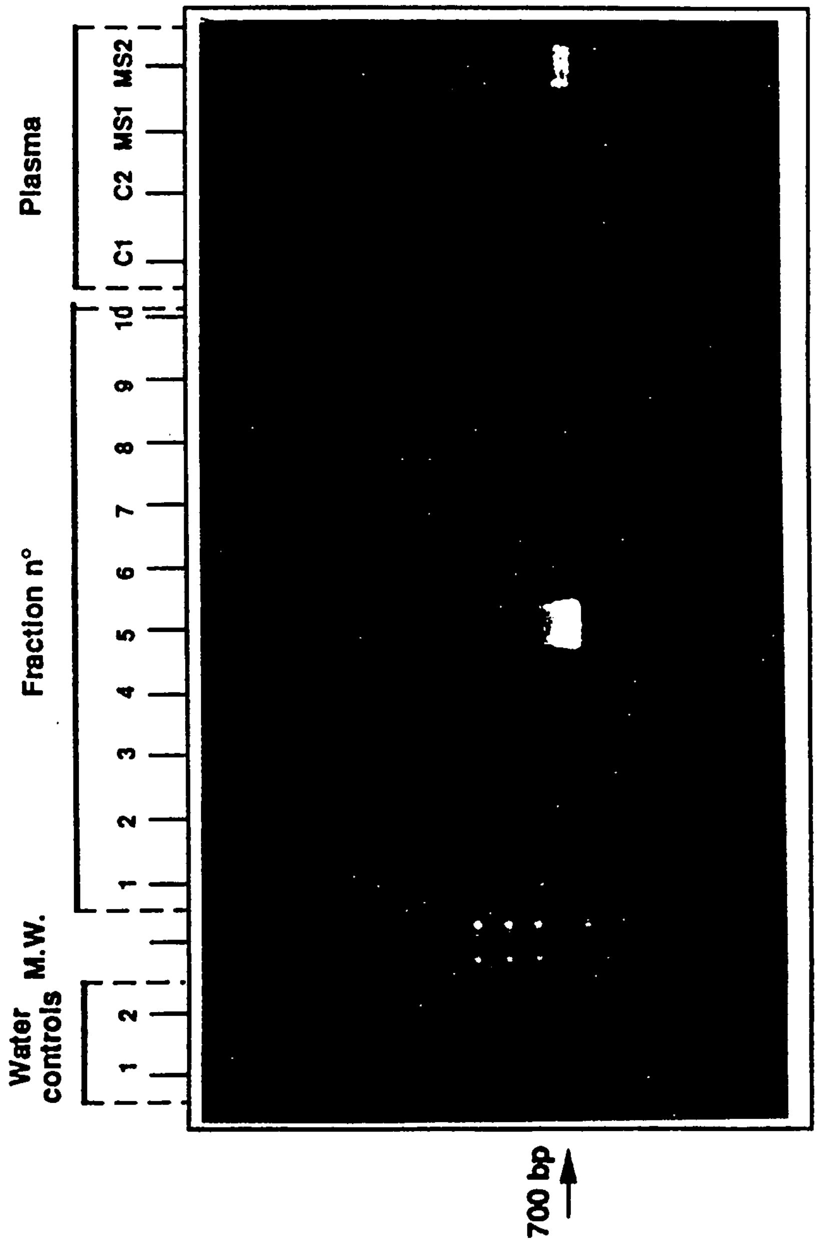

Water controls
1
2
M.W.
Fraction n°
1
2
3
4
5
6
7
8
9
10
Plasma
C1
C2
MS1
MS2
700 bp

FIG 47B

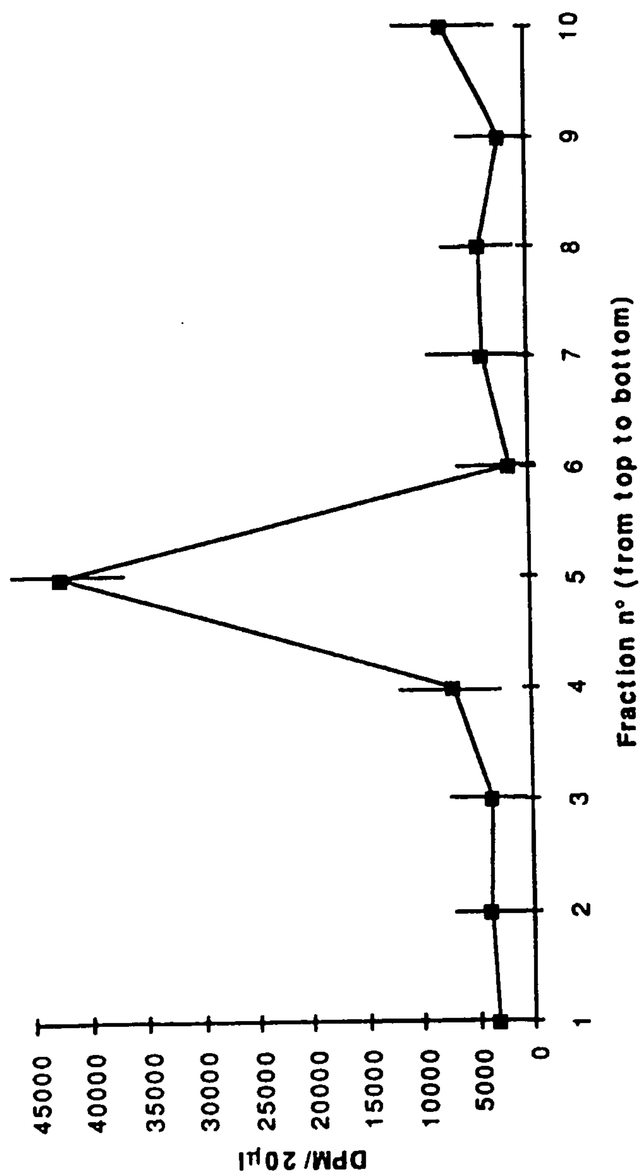

DPM/ 20µl
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
1
2
3
4
5
6
7
8
9
10
Fraction n° (from top to bottom)

FIG 48A


```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
ATGATCCAGC AGCAGGACNG AGGGTGCCCG GGGCAAGCGC CAGCCCATGC    50
M  I  Q  Q   Q  D  X   G  C  P   G  Q  A  P   A  H  A

CATCACCCTC ACAGAGCCCC AGGTATGCTT GACCATTGAG GGTCAGAAGG   100
 I  T  L   T  E  P  Q   V  C  L   T  I  E   G  Q  K  G

GTNACTGTCT CCTGGACACT GGCGGNGCCT TCTCAGTCTT ACTTTCCTGT   150
 X  C  L   L  D  T   G  G  A  F   S  V  L   L  S  C

CCTGGACAAC TGTCCTCCAG ATCTGTCACT GTCCGAGGGG TCCTAGGACA   200
P  G  Q  L   S  S  R   S  V  T   V  R  G  V   L  G  Q

GCCAGTCACT AGATACTTCT CCCAGCCACT AAGTTGTGAC TGGGGAACTT   250
 P  V  T   R  Y  F  S   Q  P  L   S  C  D   W  G  T  L

TACTCTTCCC ACATGCTTTT CTAATTATGC CTGAAAGCCC CACTCTCTTG   300
 L  F  P   H  A  F   L  I  M  P   E  S  P   T  L  L

TTGGGGAGAG ACATTCTAGC AAAAGCAGGG GCCATTATAC ATGTGAATAT   350
L  G  R  D   I  L  A   K  A  G   A  I  I  H   V  N  I

AGGAGAAGGA ACAACTGTTT GTTGTCCCCT GCTTGAGGAA GGAATTAATC   400
 G  E  G   T  T  V  C   C  P  L   L  E  E   G  I  N  P

CTGAAGTCCG GGCAACAGAA GGACAATATG GACAAGCAAA GAATGCCCGT   450
 E  V  R   A  T  E   G  Q  Y  G   Q  A  K   N  A  R

CCTGTTCAAG TTAAACTAAA GGATTCCACC TCCTTTCCCT ACCAAAGGCA   500
P  V  Q  V   K  L  K   D  S  T   S  F  P  Y   Q  R  Q
```

FIG 48B


```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
GTACCCCCTC AGACCCGAGA CCCAACAAGA ACTCCAAAAG ATTGTAAAGG    550
 Y  P  L   R  P  E  T   Q  Q  E  L  Q  K   I  V  K  D

ACCTAAAAGC CCAAGGCCTA GTAAAACCAA GCAATAGCCC TTGCAAGACT    600
  L  K  A   Q  G  L   V  K  P  S   N  S  P   C  K  T

CCAATTTTAG GAGTAAGGAA ACCCAACGGA CAGTGGAGGT TAGTGCAAGA    650
P  I  L  G   V  R  K   P  N  G   Q  W  R  L   V  Q  E

ACTCAGGATT ATCAATGAGG CTGTTGTTCC TCTATACCCA GCTGTACCTA    700
 L  R  I   I  N  E  A   V  V  P   L  Y  P   A  V  P  N

ACCCTTATAC AGTGCTTTCC CAAATACCAG AGGAAGCAGA GTGGTTTACA    750
  P  Y  T   V  L  S   Q  I  P  E   E  A  E   W  F  T

GTCCTGGACC TTAAGGATGC CTTTTTCTGC ATCCCTGTAC GTCCTGACTC    800
V  L  D  L   K  D  A   F  F  C   I  P  V  R   P  D  S

TCAATTCTTG TTTGCCTTTG AAGATCCTTT GAACCCAACG TCTCAACTCA    850
 Q  F  L   F  A  F  E   D  P  L   N  P  T   S  Q  L  T

CCTGGACTGT TTTACCCCAA GGGTTCAGGG ATAGCCCCCA TCTATTTGGC    900
 W  T  V   L  P  Q   G  F  R  D   S  P  H   L  F  G

CAGGCATTAG CCCAAGACTT GAGTCAATTC TCATACCTGG ACACTCTTGT    950
Q  A  L  A   Q  D  L   S  Q  F   S  Y  L  D   T  L  V

CCTTCAGTAC ATGGATGATT TACTTTTAGT CGCCCGTTCA GAAACCTTGT   1000
 L  Q  Y   M  D  D  L   L  L  V   A  R  S   E  T  L  C
```

FIG 48C 57/69

```
         10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
GCCATCAAGC CACCCAAGAA CTCTTAACTT TCCTCACTAC CTGTGGCTAC    1050
  H  Q  A   T  Q  E   L  L  T  F   L  T  T   C  G  Y

AAGGTTTCCA AACCAAAGGC TCGGCTCTGC TCACAGGAGA TTAGATACTN    1100
K  V  S  K   P  K  A   R  L  C   S  Q  E  I   R  Y  X

AGGGCTAAAA TTATCCAAAG GCACCAGGGC CCTCAGTGAG GAACGTATCC    1150
 G  L  K   L  S  K  G   T  R  A   L  S  E   E  R  I  Q

AGCCTATACT GGCTTATCCT CATCCCAAAA CCCTAAAGCA ACTAAGAGGG    1200
  P  I  L   A  Y  P   H  P  K  T   L  K  Q   L  R  G

TTCCTTGGCA TAACAGGTTT CTGCCGAAAA CAGATTCCCA GGTACASCCC    1250
F  L  G  I   T  G  F   C  R  K   Q  I  P  R   Y  X  P

AATAGCCAGA CCATTATATA CACTAATTAN GGAAACTCAG AAAGCCAATA    1300
 I  A  R   P  L  Y  T   L  I  X   E  T  Q   K  A  N  T

CCTATTTAGT AAGATGGACA CCTACAGAAG TGGCTTTCCA GGCCCTAAAG    1350
  Y  L  V   R  W  T   P  T  E  V   A  F  Q   A  L  K

AAGGCCCTAA CCCAAGCCCC AGTGTTCAGC TTGCCAACAG GGCAAGATTT    1400
K  A  L  T   Q  A  P   V  F  S   L  P  T  G   Q  D  F

TTCTTTATAT GCCACAGAAA AAACAGGAAT AGCTCTAGGA GTCCTTACGC    1450
 S  L  Y   A  T  E  K   T  G  I   A  L  G   V  L  T  Q

AGGTCTCAGG GATGAGCTTG CAACCCGTGG TATACCTGAG TAAGGAAATT    1500
  V  S  G   M  S  L   Q  P  V  V   Y  L  S   K  E  I
```

FIG 48D

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```
          10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
GATGTAGTGG CAAAGGGTTG GCCTCATNGT TTATGGGTAA TGGNGGCAGT    1550
D  V  V  A   K  G  W   P  H  X   L  W  V  M   X  A  V

AGCAGTCTNA GTATCTGAAG CAGTTAAAAT AATACAGGGA AGAGATCTTN    1600
 A  V  X   V  S  E  A   V  K  I   I  Q  G   R  D  L  X

CTGTGTGGAC ATCTCATGAT GTGAACGGCA TACTSRCTGC TAAAGGAGAC    1650
 V  W  T   S  H  D   V  N  G  I   L  X  A   K  G  D

TTGTGGTTGT CAGACAACCA TTTACTTAAN TAYCAGGCYY TATTACTTGA    1700
L  W  L  S   D  N  H   L  L  X   Y  Q  A  L   L  L  E

AGAGCCAGTG CTGNGACTGC GCACTTGTCC AACTCTTAAA CCCAAACTTA    1750
 E  P  V   L  X  L  R   T  C  P   T  L  K   P  K  L  M

TGCTGCCCAG AAGGATCTTT NTAGAGGTCC CCTTAGCCAA CCCTGACCTC    1800
 L  P  R   R  I  F   X  E  V  P   L  A  N   P  D  L

AACTATATAT ATACTGATGG AAGTTCGTTT GTAGAAAAGG GATTACAAAG    1850
N  Y  I  Y   T  D  G   S  S  F   V  E  K  G   L  Q  R

GGNAGGATAT NCCATAGGTG TTAGTGATAA AGCAGTACTT GAAAGTAAGC    1900
 X  G  Y   X  I  G  V   S  D  K   A  V  L   E  S  K  P

CTCTTCCCCC CCAGGGACCA GCGCCCCCGT TAGCAGAACT AGTGGCACTG    1950
 L  P  P   Q  G  P   A  P  P  L   A  E  L   V  A  L

ACCCCGCGAG CCTTAGAACT TTGGAAAGGG AGGAGGATAA ATGTGTATAC    2000
T  P  R  A   L  E  L   W  K  G   R  R  I  N   V  Y  T
```

FIG 48E

```
        10         20         30         40         50
1234567890 1234567890 1234567890 1234567890 1234567890
AGATAGCAAG TATGCTTATC TAATCCGAAA TGCCCATGTT GCAATATGGA   2050
 D  S  K   Y  A  Y  L   I  R  N   A  H  V   A  I  W  K

AAGAAAGGGA GTTCCTAACC TCTGGGGGAA CCCCCATTAA ATACCACAAG   2100
  E  R  E   F  L  T   S  G  G  T   P  I  K   Y  H  K

TTAATCATGG AGTTATTGCA CACAGTGCAA AAACTCAAGG AGGTGGAAGT   2150
L  I  M  E   L  L  H   T  V  Q   K  L  K  E   V  E  V

CTTACACTGC CAAAGCCATC AGAAAAGGGA AAGAGGGGAA GAGCAGCATA   2200
 L  H  C   Q  S  H  Q   K  R  E   R  G  E   E  Q  H  K

AGTGGCTACA GAGGCAAGGA AAGACTAGCA GAAAGGAAAG AGAGAAAGAG   2250
  W  L  Q   R  Q  G   K  T  S  R   K  E  R   E  K  E

ACAGAAAGTC AGAGAGAGAG AGAGGAAGAG ACAGAGCACA AAGAGGGAGT   2300
T  E  S  Q   R  E  R   E  E  E   T  E  H  K   E  G  V

CAGAGAGAGA GAGAGACAGA GAGTCAGAGA GAAGGAAAGA GAGAGAGGAA   2350
 R  E  R   E  R  Q  R   V  R  E   K  E  R   E  R  G  R

GAGACAAAGA ATGA                                          2364
  D  K  E   .
```

FIG 49A

```
Complement of 8/46-7 propre      GACTTGAGCC AGTCCTCATA CCTGGACATT CTTGTTCATC AGTATAGGGA    50
1 /46-7 propre                   GACTTGAGCC AGTCCTCATA CCTGGACATT CTTGTTCATC AGTATGGGGA    50
Complement of c15 propre 46-7    GACTTGAGCC AGTCCTCATA CCTGGACATT CTTGTTCCTC AGTATGGGGA    50
Consensus                        GACTTGAGCC AGTCCTCATA CCTGGACATT CTTGTTCMTC AGTATRGGGA    50

Complement of 8/46-7 propre      TGAATTAATT ATAGCCACCC ATTCAGAAAC CTTGTGGCAT CAAGCCACCC   100
1 /46-7 propre                   TGACTTAATT ATAGCCACCC ATTCAGAAAC CTTGTGGCAT CAAGCCACCC   100
Complement of c15 propre 46-7    TGAATTAATT ATAGCCACCC ATTCAGAAAC CTTGTGGCAC CAAGCCACCC   100
Consensus                        TGAMTTAATT ATAGCCACCC ATTCAGAAAC CTTGTGGCAY CAAGCCACCC   100

Complement of 8/46-7 propre      AAGAGCTCTT AAATTTCCTC GCTACCTGTG GCTCCAAACA AAGGGCTCAG   150
1 /46-7 propre                   AAGCGCTCTT AAATTTCCTT GCTACCTGTG GCTCCAAACA AAAGGCTCAC   150
Complement of c15 propre 46-7    AAGCGCTCTT AAATTTCCTC GCTACCTGTG GCTCCAAACA AAAGGCTCAG   150
Consensus                        AAGMGCTCTT AAATTTCCTY GCTACCTGTG GCTCCAAACA AARGGCTCAS   150

Complement of 8/46-7 propre      CTCTGCTCAC AGCAGGTTAA ATACTTAGGG CTAAAATTAT CCAAAGTCGC   200
1 /46-7 propre                   CTCTGCTCAC ACCAGGTTAA ATACTTAGGG CTAAAATTAT CCAAAGTCAC   200
Complement of c15 propre 46-7    CTCTGCTCAC AGCAGGTTAA ATACTTAGGG CTAAAATTAT CCAAAGTCAC   200
Consensus                        CTCTGCTCAC ASCAGGTTAA ATACTTAGGG CTAAAATTAT CCAAAGTCRC   200

Complement of 8/46-7 propre      CAGGGCCCTC AGAGAGGAAC GTATCCAGCG TATACTGGAT TATCCACATC   250
1 /46-7 propre                   CAGGGCCCTC AGAGAGGAAC GTATCCAGCG TATACTGGCT TATCCACATC   250
Complement of c15 propre 46-7    CAGGGCCCTC AGAGAGGAAC GTATCCAGCG TATACTGGCT TATCCCCATC   250
Consensus                        CAGGGCCCTC AGAGAGGAAC GTATCCAGCG TATACTGGMT TATCCMCATC   250

Complement of 8/46-7 propre      CCAAAACCAT AAAGCAACTA AGAGGGTTCC TTGGCATAAC AGCCTTCTGC   300
1 /46-7 propre                   CCATAACCCT AAAGCAACTA AGAGGGTTCC TTGGCATATC AGCCTTCTGC   300
Complement of c15 propre 46-7    CCAAAACCCT AAAGCAACTA AGAAGGTTCC TTGGCATAAC AGCCTTCTGC   300
Consensus                        CCAWAACCMT AAAGCAACTA AGARGGTTCC TTGGCATAWC AGCCTTCTGC   300

Complement of 8/46-7 propre      CGAATATGGA TTCCCCGATA CAGAGAAATA GCCAGGCCAT TATGTACATT   350
1 /46-7 propre                   CGAATATGGA TTCCCCGATA CAGAGAAATA GCCAGGCCAT TATGTACATT   350
Complement of c15 propre 46-7    CGAATATGGA TTCCCAGATA CAGCGAAATA GCCAGGCCAT TATGTACATT   350
Consensus                        CGAATATGGA TTCCCMGATA CAGMGAAATA GCCAGGCCAT TATGTACATT   350

Complement of 8/46-7 propre      AGTTAAGGAA ACTCAGAAAG CCAATACCCA TATAGTAAGA TGGACACCTG   400
1 /46-7 propre                   AATTAAGGAA ACTCAGAAAG CCAATACCCA TATAGTAAGA TGGACACCTG   400
Complement of c15 propre 46-7    ATCTAAGGAA ACTCAGAAAG CCAATACCCA TATAGTAAGA TGGACACCTG   400
Consensus                        ADYTAAGGAA ACTCAGAAAG CCAATACCCA TATAGTAAGA TGGACACCTG   400

Complement of 8/46-7 propre      AGACAGAAGT GGCTTTCCAG GCCCTAAAG                           429
1 /46-7 propre                   AAACAGAAGT GGCTTTCCAG GCCCTAAAG                           429
Complement of c15 propre 46-7    AAACAGAAGT GGCTTTCCAG GCCCTAAAG                           429
Consensus                        ARACAGAAGT GGCTTTCCAG GCCCTAAAG                           429
```

FIG 49B

Trans of 1 /46-7 pr	DLSQSSYLDI LVLQYGDDLI IATHSETLWH QATQALLNFL ATCGSKQKAH	50
Trans of Complement-2 (8)	DLSQSSYLDI LVLQYRDDLI IATHSETLWH QATQVLLNFL ATCGSKQRAQ	50
Trans of Complement (5)	DLSQSSYLDI LVFQYGDDLI IATHSETLWH QATQALLNFL ATCGSKQKAQ	50
Consensus	DLSQSSYLDI LVLQYGDDLI IATHSETLWH QATQALLNFL ATCGSKQKAQ	50

Trans of 1 /46-7 pr	LCSHQVKYLG LKLSKVIRAL REERIQRILA YPHPITIKQL RGFLGISAFC	100
Trans of Complement-2	LCSQQVKYLG LKLSKVARAL REERIQRILD YPHPKTIKQL RGFLGIIAFC	100
Trans of Complement	LCSQQVKYLG LKLSKVIRAL REERIQRILA YPHPKTIKQL RKFLGIIAFC	100
Consensus	LCSQQVKYLG LKLSKVIRAL REERIQRILA YPHPKTIKQL RGFLGIIAFC	100

Trans of 1 /46-7 pr	RIWIPGYSEI ARPLCTLIKE TQKANTHIVR WTPETEVAFQ ALK	143
Trans of Complement-2	RIWIPRYSEI ARPLCTLMKE TQKANTHIVR WTPETEVAFQ ALK	143
Trans of Complement	RIWIPRYSEI ARPLCTLSKE TQKANTHIVR WTPETEVAFQ ALK	143
Consensus	RIWIPRYSEI ARPLCTL KE TQKANTHIVR WTPETEVAFQ ALK	143

FIG 50B

Trans of c143 propr	DLSQSSYLDX LVLRYMDDLL LATHSETLCH QATQALLNFL ATCGYKVSKP	50
Trans of 42/68-1 pr	DLSQSSYLDT LVLRYMDDLL LATHSETLCH QATQALLNFL ATCGYKVSKP	50
Trans of 41/68-1 pr	DLSQSSYLDT LVLRYMDDLL LATHSETLCH QATQALLNFL ATCGYKVSKP	50
Consensus	DLSQSSYLDT LVLRYMDDLL LATHSETLCH QATQALLNFL ATCGYKVSKP	50

Trans of c143 propr	KAQLCSQQVK YLGLKLSKGT RTLSEERIQP ILGYPHPKTL KQLTAFLGIT	100
Trans of 42/68-1 pr	KAQLCSQQVK YLGLKLSKGT RTLSEERIQP ILGYPHPKTL KQLTAFLGIT	100
Trans of 41/68-1 pr	KAQLCSQQVK YLGLKLSKGT RTLSEERIQP ILGYPHPKTL KQLTAFLGIT	100
Consensus	KAQLCSQQVK YLGLKLSKGT RTLSEERIQP ILGYPHPKTL KQLTAFLGIT	100

Trans of c143 propr	GFCQIWIPRY SKIARPLNTR IKETQKANTH LVRWISEAEV AFQALK	146
Trans of 42/68-1 pr	GFCQIWIPRY SKVARPLNTR IKETQKASTH LVRWITEAEV AFQALK	146
Trans of 41/68-1 pr	GFCQIWIPRY SKIARPLNTR IKETQKANTH LVRWITEAEV AFQALK	146
Consensus	GFCQIWIPRY SKIARPLNTR IKETQKANTH LVRWITEAEV AFQALK	146

FIG 50 A

```
41/68-1 propre      GACTTGAGCC AGTCCTCATA CCTGGACACT CTTGTCCTTC GGTACATGGA   50
c143 propre 68-1    GACTTGAGCC AGTCATCATA CCTGGACAAT CTTGTCCTTC GGTACATGGA   50
42/68-1 propre      GACTTGAGCC AGTCCTCATA CCTGGACACT CTTGTCCTTC GGTACATGGA   50
Consensus           GACTTGAGCC AGTCMTCATA CCTGGACAMT CTTGTCCTTC GGTACATGGA   50

41/68-1 propre      TGATTTACTT TTAGCCACCC ATTCAGAAAC CTTGTGCCAT CAAGCCACCC  100
c143 propre 68-1    TGATTTACTT TTAGCCACCC ATTCAGAAAC CTTGTGCCAT CAAGCCACCC  100
42/68-1 propre      TGATTTACTT TTAGCCACCC ATTCAGAAAC CTTGTGCCAT CAAGCCACCC  100
Consensus           TGATTTACTT TTAGCCACCC ATTCAGAAAC CTTGTGCCAT CAAGCCACCC  100

41/68-1 propre      AAGCACTCTT AAATTTCCTT GCTACCTGTG GCTACAAGGT TTCCAAACCA  150
c143 propre 68-1    AAGCACTCTT AAATTTCCTT GCTACCTGTG GCTACAAGGT TTCCAAACCA  150
42/68-1 propre      AAGCACTCTT AAATTTCCTT GCTACCTGTG GCTACAAGGT TTCCAAACCA  150
Consensus           AAGCACTCTT AAATTTCCTT GCTACCTGTG GCTACAAGGT TTCCAAACCA  150

41/68-1 propre      AAGGCTCAGC TCTGCTCACA GCAGGTTAAA TACTTAGGGC TAAAATTATC  200
c143 propre 68-1    AAGGCTCAGC TCTGCTCACA GCAGGTTAAA TACTTAGGGC TAAAATTATC  200
42/68-1 propre      AAGGCTCAGC TCTGCTCACA GCAGGTTAAA TACTTAGGGC TAAAATTATC  200
Consensus           AAGGCTCAGC TCTGCTCACA GCAGGTTAAA TACTTAGGGC TAAAATTATC  200

41/68-1 propre      CAAAGGCACC AGAACCCTCA GTGAGGAACG TATCCAGCCT ATACTGGGTT  250
c143 propre 68-1    CAAAGGCACC AGAACCCTCA GTGAGGAACG TATCCAGCCT ATACTGGGTT  250
42/68-1 propre      CAAAGGCACC AGAACCCTCA GTGAGGAACG TATCCAGCCT ATACTGGGTT  250
Consensus           CAAAGGCACC AGAACCCTCA GTGAGGAACG TATCCAGCCT ATACTGGGTT  250

41/68-1 propre      ATCCTCATCC CAAAACCCTA AAGCAACTAA CAGCGTTCCT TGGCATAACA  300
c143 propre 68-1    ATCCTCATCC CAAAACCCTA AAGCAACTAA CAGCGTTCCT TGGCATAACA  300
42/68-1 propre      ATCCTCATCC CAAAACCCTA AAGCAACTAA CAGCGTTCCT TGGCATAACA  300
Consensus           ATCCTCATCC CAAAACCCTA AAGCAACTAA CAGCGTTCCT TGGCATAACA  300

41/68-1 propre      GGTTTCTGCC AAATATGGAT TCCCAGGTAC AGCAAGATAG CCAGACCATT  350
c143 propre 68-1    GGTTTCTGCC AAATATGGAT TCCCAGGTAC AGCAAAATAG CCAGACCATT  350
42/68-1 propre      GGTTTCTGCC AAATATGGAT TCCCAGGTAC AGCAAAGTAG CCAGACCATT  350
Consensus           GGTTTCTGCC AAATATGGAT TCCCAGGTAC AGCAARRTAG CCAGACCATT  350

41/68-1 propre      AAATACACGA ATTAAGGAAA CTCAAAAAGC CAATACCCAT TTAGTAAGAT  400
c143 propre 68-1    AAATACACGA ATTAAGGAAA CTCAAAAAGC CAATACCCAT TTAGTAAGAT  400
42/68-1 propre      AAATACACGA ATTAAGGAAA CTCAAAAAGC CAGTACCCAT TTAGTAAGAT  400
Consensus           AAATACACGA ATTAAGGAAA CTCAAAAAGC CARTACCCAT TTAGTAAGAT  400

41/68-1 propre      GGACACCTGA AGCAGAAGTG GCTTTCCAGG CCCTAAAG               438
c143 propre 68-1    GGACATCTGA AGCAGAAGTG GCTTTCCAGG CCCTAAAG               438
42/68-1 propre      GGACACCTGA AGCAGAAGTG GCTTTCCAGG CCCTAAAG               438
Consensus           GGACAYCTGA AGCAGAAGTG GCTTTCCAGG CCCTAAAG               438
```

FIG 51A

```
MSRV pol          ATTATGCCTG AAAGCCCCAC TCCCTTGTTA GGGAGAGACA TTTTAGCAAA    50
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------
Consensus         ATTATGCCTG AAAGCCCCAC TCCCTTGTTA GGGAGAGACA TTTTAGCAAA    50

MSRV pol          AGCAGGGGCC ATTATACACC TGAACATAGG AAAAGGAATA CCCATTTGCT   100
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------
Consensus         AGCAGGGGCC ATTATACACC TGAACATAGG AAAAGGAATA CCCATTTGCT   100

MSRV pol          GTCCCCTGCT TGAGGAAGGA ATTAATCCTG AAGTCTGGGC AATAGAAGGA   150
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------
Consensus         GTCCCCTGCT TGAGGAAGGA ATTAATCCTG AAGTCTGGGC AATAGAAGGA   150

MSRV pol          CAATATGGAC AAGCAAAGAA TGCCCGTCCT GTTCAAGTTA AACTAAAGGA   200
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------
Consensus         CAATATGGAC AAGCAAAGAA TGCCCGTCCT GTTCAAGTTA AACTAAAGGA   200

MSRV pol          TTCTGCCTCC TTTCCCTACC AAAGGAAGTA CCCTCTTAGA CCCGAGGCCC   250
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------
Consensus         TTCTGCCTCC TTTCCCTACC AAAGGAAGTA CCCTCTTAGA CCCGAGGCCC   250

MSRV pol          TACAAGGANC TCAAAAGATT GTTAAGGACC TAAAAGCCCA AGGCCTAGTA   300
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------
Consensus         TACAAGGANC TCAAAAGATT GTTAAGGACC TAAAAGCCCA AGGCCTAGTA   300

MSRV pol          AAACCATGCA GTAGCCCCTG CAATACTCCA ATTTTAGGAG TAAGGAAACC   350
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------
Consensus         AAACCATGCA GTAGCCCCTG CAATACTCCA ATTTTAGGAG TAAGGAAACC   350

MSRV pol          CAACGGACAG TGGAGGTTAG TGCAAGATCT CAGGATTATT AATGAGGCTG   400
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------
Consensus         CAACGGACAG TGGAGGTTAG TGCAAGATCT CAGGATTATT AATGAGGCTG   400

MSRV pol          TTTTTCCTCT ATACCCAGCT GTATCTAGCC CTTATACTCT GCTTTCCCTA   450
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------
Consensus         TTTTTCCTCT ATACCCAGCT GTATCTAGCC CTTATACTCT GCTTTCCCTA   450

MSRV pol          ATACCAGAGG AAGCAGAGTG GTTTACAGTC CTGGACCTTA AGGATGCCTT   500
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------
Consensus         ATACCAGAGG AAGCAGAGTG GTTTACAGTC CTGGACCTTA AGGATGCCTT   500

MSRV pol          TTTCTGCATC CCTGTACGTC CTGACTCTCA ATTCTTGTTT GCCTTTGAAG   550
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------
Consensus         TTTCTGCATC CCTGTACGTC CTGACTCTCA ATTCTTGTTT GCCTTTGAAG   550

MSRV pol          ATCCTTTGAA CCCAACGTCT CAACTCACCT GGACTGTTTT ACCCCAAGGG   600
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------
Consensus         ATCCTTTGAA CCCAACGTCT CAACTCACCT GGACTGTTTT ACCCCAAGGG   600

MSRV pol          TTCAGGGATA GCCCCCATCT ATTTGGCCAG GCATTAGCCC AAGACTTGAG   650
cons ADN 1,5,8    ---------- ---------- ---------- ---------- --GACTTGAG     8
Consensus         TTCAGGGATA GCCCCCATCT ATTTGGCCAG GCATTAGCCC AAGACTTGAG   650

MSRV pol          TCAATACTCA TACCTGGACA ATCTTGTACT TCAGTACGTG GATGAATTAC   700
cons ADN 1,5,8    CCAGTCCTCA TACCTGGACA CTCTTGTCCY TCAGTATRGG GATGAMTTAA    58
Consensus         YCARTMCTCA TACCTGGACA MTCTTGTMCY TCAGTAYRKG GATGAMTTAM   700

MSRV pol          TTTTAGACGC CCGTTCAGAA ACCTTGTGCC AACAAGCCAC CCAAGAACTC   750
cons ADN 1,5,8    TTATAGCCAC CCATTCAGAA ACCTTGTGGC AMCAAGCCAC CCAAGYGCTC   108
Consensus         TTWTAGMCRC CCRTTCAGAA ACCTTGTGSC AMCAAGCCAC CCAAGHRCTC   750

MSRV pol          TTAACTTTCC TCACTACCTG TGGCTACAAG GTTTCCAAAC CAAAGGCTCG   800
cons ADN 1,5,8    TTAAATTTCC TYGCTACCTG TGGCT----- ----CCAAAC AAAAGGCTCA   149
Consensus         TTAAMTTTCC TYRCTACCTG TGGCTACAAG GTTTCCAAAC MAAAGGCTCR   800
```

FIG 51 A (cont.)

```
MSRV pol          GCTCTGCTCA CAGGAGGTTA GATACTTAGG GCTAAAATTA TCCAAAGGCA   850
cons ADN 1,5,8    SCTCTGCTCA CASCAGGTTA RATACTTAGG GCTAAAATTA TCCAAAGTCR   199
Consensus         SCTCTGCTCA CASSAGKTTA RATACTTAGG GCTAAAATTA TCCAAAGKCR   850

MSRV pol          CCAGGGCCCT CAGTGAGGAA CGTATCCAGC CTATACTGGC TTATCCTCAT   900
cons ADN 1,5,8    CCAGGGCCCT CAGAGAGGAA CGTATCCAGC GTATACTGGM TTATCCMCAT   249
Consensus         CCAGGGCCCT CAGWGAGGAA CGTATCCAGC STATACTGGM TTATCCMCAT   900

MSRV pol          CCCAAAACCC TAAAGCAACT AAGAGGGTTC CTTGGCATAA CAGGTTTCTG   950
cons ADN 1,5,8    CCCAWAACCM TAAAGCAACT AAGARGGTTC CTTGGCATAW CAGCCTTCTG   299
Consensus         CCCAWAACCM TAAAGCAACT AAGARGGTTC CTTGGCATAW CAGSYTTCTG   950

MSRV pol          CCGAAAACAG ATTCCCAGGT ACACCCCAAT AGCCAGACCA TTATATACAC  1000
cons ADN 1,5,8    CCGAATATGG ATTCCCTGAT ACAGYGAAAT AGCCAGGCCA TTATGTACAT   349
Consensus         CCGAAWAYRG ATTCCCWGRT ACASYSMAAT AGCCAGRCCA TTATRTACAY  1000

MSRV pol          TAATTAGGGA AACTCAGAAA GCCAATACCT ATTTAGTAAG ATGGACACCT  1050
cons ADN 1,5,8    TADYTAAGGA AACTCAGAAA GCCAATACCC ATATAGTAAG ATGGACACCT   399
Consensus         TADYTARGGA AACTCAGAAA GCCAATACCY ATWTAGTAAG ATGGACACCT  1050

MSRV pol          ---ACAGAAG TGGCTTTCCA GGCCCTAAAG AAGGCCCTAA CCCAAGCCCC  1097
cons ADN 1,5,8    GARACAGAAG TGGCTTTCCA GGCCCTAAAG ---------- ----------   429
Consensus         GARACAGAAG TGGCTTTCCA GGCCCTAAAG AAGGCCCTAA CCCAAGCCCC  1100

MSRV pol          AGTGTTCAGC TTGCCAACAG GGCAAGATTT TTCTTTATAT GCCACAGAAA  1147
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------   429
Consensus         AGTGTTCAGC TTGCCAACAG GGCAAGATTT TTCTTTATAT GCCACAGAAA  1150

MSRV pol          AAACAGGAAT AGCTCTAGGA GTCCTTACGC AGGTCTCAGG GATGAGCTTG  1197
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------   429
Consensus         AAACAGGAAT AGCTCTAGGA GTCCTTACGC AGGTCTCAGG GATGAGCTTG  1200

MSRV pol          CAACCCGTGG TATACCTGAG TAAGGAAATT GATGTAGTGG CAAAGGGTTG  1247
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------   429
Consensus         CAACCCGTGG TATACCTGAG TAAGGAAATT GATGTAGTGG CAAAGGGTTG  1250

MSRV pol          GCCTCATTGT TTATGGGTAA TGGCGGCAGT AGCAGTCTTA GTATCTGAAG  1297
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------   429
Consensus         GCCTCATTGT TTATGGGTAA TGGCGGCAGT AGCAGTCTTA GTATCTGAAG  1300

MSRV pol          CAGTTAAAAT AATACAGGGA AGAGATCTTA CTGTGTGGAC ATCTCATGAT  1347
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------   429
Consensus         CAGTTAAAAT AATACAGGGA AGAGATCTTA CTGTGTGGAC ATCTCATGAT  1350

MSRV pol          GTGAACGGCA TACTCACTGC TAAAGGAGAC TTGTGGTTGT CAGACAACCA  1397
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------   429
Consensus         GTGAACGGCA TACTCACTGC TAAAGGAGAC TTGTGGTTGT CAGACAACCA  1400

MSRV pol          TTTACTTAAT TATCAGGCTC TATTACTTGA AGAGCCAGTG CTGAGACTGC  1447
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------   429
Consensus         TTTACTTAAT TATCAGGCTC TATTACTTGA AGAGCCAGTG CTGAGACTGC  1450

MSRV pol          GCACTTGTGC AACTCTTAAA CCCGCCACAT TTCTTCCAGA CAATGAAGAA  1497
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------   429
Consensus         GCACTTGTGC AACTCTTAAA CCCGCCACAT TTCTTCCAGA CAATGAAGAA  1500

MSRV pol          AAGATAGAAC ATAACTGTCA ACAAGTAATT GCTCAAACCT ATGCTGCTCG  1547
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------   429
Consensus         AAGATAGAAC ATAACTGTCA ACAAGTAATT GCTCAAACCT ATGCTGCTCG  1550

MSRV pol          AGGGGACCTT CTAGAGGTTC CCTTGACTGA TCCCGACCTC AACTTGTATA  1597
cons ADN 1,5,8    ---------- ---------- ---------- ---------- ----------   429
Consensus         AGGGGACCTT CTAGAGGTTC CCTTGACTGA TCCCGACCTC AACTTGTATA  1600
```

FIG 51 B

```
Trans of MSRV pol   IMPESPTPLL GRDILAKAGA IIHLNIGKGI PICCPLLEEG INPEVWAIEG    50
cons prot 1,5,8     ---------- ---------- ---------- ---------- ----------
Consensus           .......... .......... .......... .......... ..........    50

Trans of MSRV pol   QYGQAKNARP VQVKLKDSAS FPYQRKYPLR PEALQGXQKI VKDLKAQGLV   100
cons prot 1,5,8     ---------- ---------- ---------- ---------- ----------
Consensus           .......... .......... .......... .......... ..........   100

Trans of MSRV pol   KPCSSPCNTP ILGVRKPNGQ WRLVQDLRII NEAVFPLYPA VSSPYTLLSL   150
cons prot 1,5,8     ---------- ---------- ---------- ---------- ----------
Consensus           .......... .......... .......... .......... ..........   150

Trans of MSRV pol   IPEEAEWFTV LDLKDAFFCI PVRPDSQFLF AFEDPLNPTS QLTWTVLPQG   200
cons prot 1,5,8     ---------- ---------- ---------- ---------- ----------
Consensus           .......... .......... .......... .......... ..........   200

Trans of MSRV pol   FRDSPHLFGQ ALAQDLSQHS YLDILVLQYV DDLLLVARSE TLHHQATQEL   250
cons prot 1,5,8     ---------- ----DLSQHS YLDILVLQYG DDLLIATHSE TLWHQATQAL    36
Consensus           .......... ....DLSQ.S YLD.LVLQY. DDL.....SE TL.HQATQ.L   250

Trans of MSRV pol   LIFLITCGMK VSKEKARLCS QEIRYLGKLL SKETRALSEE RIQEILAYPH   300
cons prot 1,5,8     LNFLATCGSK ---QKAQLCS QQVKYLGKLL SKVTRALREE RIQRILAYPH    83
Consensus           L.FL.TCG.K ...KA.LCS. Q...YLGKL. SK.TRAL.EE RIQ.ILAYPH   300

Trans of MSRV pol   PKTLKQLRGF LGITGFCRKQ IPRYTHIARP LMTLIRETQK ANTYLVRWTP   350
cons prot 1,5,8     PKTLKQLRGF LGITAFCRIW IPRYSHIARP LLTLKKETQK ANTHIVRWTP   133
Consensus           PKTLKQLRGF LGIT.FCR.. IPRY..IARP L.TL..ETQK ANT..VRWTP   350

Trans of MSRV pol   -TEVAFQALK KALTQAPVFS LPTGQDFSLY ATEKTGIALG VLTQVSGMSL   399
cons prot 1,5,8     ETEVAFQALK ---------- ---------- ---------- ----------   143
Consensus           .TEVAFQALK .......... .......... .......... ..........   400

Trans of MSRV pol   QPVVYLSKEI DVVAKGWPHC LWVMAAVAVL VSEAVKIIQG RDLTVWTSHD   449
cons prot 1,5,8     ---------- ---------- ---------- ---------- ----------   143
Consensus           .......... .......... .......... .......... ..........   450

Trans of MSRV pol   VNGILTAKGD LWLSDNHLLN YQALLLEEPV LRLRTCATLK PATFLPDNEE   499
cons prot 1,5,8     ---------- ---------- ---------- ---------- ----------   143
Consensus           .......... .......... .......... .......... ..........   500

Trans of MSRV pol   KIEHNCQQVI AQTYAARGDL LEVPLTDPDL NLYTDGSSLA EKGLRKAGYA   549
cons prot 1,5,8     ---------- ---------- ---------- ---------- ----------   143
Consensus           .......... .......... .......... .......... ..........   550

Trans of MSRV pol   VISDNGILES NRLTPGTSAH LAELIALTWA LELGEGKRVN IYSDSKYAYL   599
cons prot 1,5,8     ---------- ---------- ---------- ---------- ----------   143
Consensus           .......... .......... .......... .......... ..........   600

Trans of MSRV pol   VLHAHAAIWR EREFLTSEGT PINHQEAIRR LLLAVQKPKE VAVLHCQGHQ   649
cons prot 1,5,8     ---------- ---------- ---------- ---------- ----------   143
Consensus           .......... .......... .......... .......... ..........   650

Trans of MSRV pol   EEEEREIEGN RQADIEAKKA ARQDSPLEML IEGP                     683
cons prot 1,5,8     ---------- ---------- ---------- ----                     143
Consensus           .......... .......... .......... ....                     684
```

FIG 52 A

```
MSRV pol          ATTATGCCTG AAAGCCCCAC TCCCTTGTTA GGGAGAGACA TTTTAGCAAA   50
cons ADN 41,42,43 ---------- ---------- ---------- ---------- ----------
Consensus         ATTATGCCTG AAAGCCCCAC TCCCTTGTTA GGGAGAGACA TTTTAGCAAA   50

MSRV pol          AGCAGGGGCC ATTATACACC TGAACATAGG AAAAGGAATA CCCATTTGCT  100
cons ADN 41,42,43 ---------- ---------- ---------- ---------- ----------
Consensus         AGCAGGGGCC ATTATACACC TGAACATAGG AAAAGGAATA CCCATTTGCT  100

MSRV pol          GTCCCCTGCT TGAGGAAGGA ATTAATCCTG AAGTCTGGGC AATAGAAGGA  150
cons ADN 41,42,43 ---------- ---------- ---------- ---------- ----------
Consensus         GTCCCCTGCT TGAGGAAGGA ATTAATCCTG AAGTCTGGGC AATAGAAGGA  150

MSRV pol          CAATATGGAC AAGCAAAGAA TGCCCGTCCT GTTCAAGTTA AACTAAAGGA  200
cons ADN 41,42,43 ---------- ---------- ---------- ---------- ----------
Consensus         CAATATGGAC AAGCAAAGAA TGCCCGTCCT GTTCAAGTTA AACTAAAGGA  200

MSRV pol          TTCTGCCTCC TTTCCCTACC AAAGGAAGTA CCCTCTTAGA CCCGAGGCCC  250
cons ADN 41,42,43 ---------- ---------- ---------- ---------- ----------
Consensus         TTCTGCCTCC TTTCCCTACC AAAGGAAGTA CCCTCTTAGA CCCGAGGCCC  250

MSRV pol          TACAAGGANC TCAAAAGATT GTTAAGGACC TAAAAGCCCA AGGCCTAGTA  300
cons ADN 41,42,43 ---------- ---------- ---------- ---------- ----------
Consensus         TACAAGGANC TCAAAAGATT GTTAAGGACC TAAAAGCCCA AGGCCTAGTA  300

MSRV pol          AAACCATGCA GTAGCCCCTG CAATACTCCA ATTTTAGGAG TAAGGAAACC  350
cons ADN 41,42,43 ---------- ---------- ---------- ---------- ----------
Consensus         AAACCATGCA GTAGCCCCTG CAATACTCCA ATTTTAGGAG TAAGGAAACC  350

MSRV pol          CAACGGACAG TGGAGGTTAG TGCAAGATCT CAGGATTATT AATGAGGCTG  400
cons ADN 41,42,43 ---------- ---------- ---------- ---------- ----------
Consensus         CAACGGACAG TGGAGGTTAG TGCAAGATCT CAGGATTATT AATGAGGCTG  400

MSRV pol          TTTTTCCTCT ATACCCAGCT GTATCTAGCC CTTATACTCT GCTTTCCCTA  450
cons ADN 41,42,43 ---------- ---------- ---------- ---------- ----------
Consensus         TTTTTCCTCT ATACCCAGCT GTATCTAGCC CTTATACTCT GCTTTCCCTA  450

MSRV pol          ATACCAGAGG AAGCAGAGTG GTTTACAGTC CTGGACCTTA AGGATGCCTT  500
cons ADN 41,42,43 ---------- ---------- ---------- ---------- ----------
Consensus         ATACCAGAGG AAGCAGAGTG GTTTACAGTC CTGGACCTTA AGGATGCCTT  500

MSRV pol          TTTCTGCATC CCTGTACGTC CTGACTCTCA ATTCTTGTTT GCCTTTGAAG  550
cons ADN 41,42,43 ---------- ---------- ---------- ---------- ----------
Consensus         TTTCTGCATC CCTGTACGTC CTGACTCTCA ATTCTTGTTT GCCTTTGAAG  550

MSRV pol          ATCCTTTGAA CCCAACGTCT CAACTCACCT GGACTGTTTT ACCCCAAGGG  600
cons ADN 41,42,43 ---------- ---------- ---------- ---------- ----------
Consensus         ATCCTTTGAA CCCAACGTCT CAACTCACCT GGACTGTTTT ACCCCAAGGG  600

MSRV pol          TTCAGGGATA GCCCCCATCT ATTTGGCCAG GCATTAGCCC AAGACTTGAG  650
cons ADN 41,42,43 ---------- ---------- ---------- ---------- --GACTTGAG    8
Consensus         TTCAGGGATA GCCCCCATCT ATTTGGCCAG GCATTAGCCC AAGACTTGAG  650

MSRV pol          TCAATTCTCA TACCTGGACA ATCTTGTCCT TCAGTACGTG GATGATTTAC  700
cons ADN 41,42,43 CCAGTCYTCA TACCTGGACA CTCTTGTCCT TCGGTACATG GATGATTTAC   58
Consensus         YCARTYYTCA TACCTGGACA MTCTTGTCCT TCRGTACRTG GATGATTTAC  700

MSRV pol          TTTTAGTCGC CCATTCAGAA ACCTTGTGCC ATCAAGCCAC CCAAGAACTC  750
cons ADN 41,42,43 TTTTAGCCAC CCGTTCAGAA ACCTTGTGCC ATCAAGCCAC CCAAGCACTC  108
Consensus         TTTTAGYCRC CCRTTCAGAA ACCTTGTGCC ATCAAGCCAC CCAAGMACTC  750

MSRV pol          TTAACTTTCC TCACTACCTG TGGCTACAAG GTTTCCAAAC CAAAGGCTGG  800
cons ADN 41,42,43 TTAAATTTCC TTGCTACCTG TGGCTACAAG GTTTCCAAAC CAAAGGCTCA  158
Consensus         TTAAMTTTCC TYRCTACCTG TGGCTACAAG GTTTCCAAAC CAAAGGCTSR  800
```

FIG 52A (cont.,

MSRV pol	GCTCTGCTCA CAGGAGGTTA GATACTTAGG GCTAAAATTA TCCAAAGGCA	850
cons ADN 41,42,43	GCTCTGCTCA CAGCAGATTA AATACTTAGG GCTAAAATTA TCCAAAGGCA	208
Consensus	GCTCTGCTCA CAGSAGRTTA RATACTTAGG GCTAAAATTA TCCAAAGGCA	850
MSRV pol	CCAGGGCCCT CAGTGAGGAA CGTATCCAGC CTATACTGGC TTATCCTCAT	900
cons ADN 41,42,43	CCAGAACCCT CAGTGAGGAA CGTATCCAGC CTATACTGGG TTATCCTCAT	258
Consensus	CCAGRRCCCT CAGTGAGGAA CGTATCCAGC CTATACTGGS TTATCCTCAT	900
MSRV pol	CCCAAAACCC TAAAGCAACT AAGAGGGTTC CTTGGCATAA CAGGTTTCTG	950
cons ADN 41,42,43	CCCAAAACCC TAAAGCAACT AACAGCGTTC CTTGGCATAA CAGGTTTCTG	308
Consensus	CCCAAAACCC TAAAGCAACT AASAGSGTTC CTTGGCATAA CAGGTTTCTG	950
MSRV pol	CCGAAAACAG ATTCCCAGGT ACAGCCAAAT AGCCAGACCA TTAGATACAC	1000
cons ADN 41,42,43	CCAAATATGG ATTCCCAGGT ACACCAARRT AGCCAGACCA TTAAATACAC	358
Consensus	CCRAAWAYRG ATTCCCAGGT ACASCMMRRT AGCCAGACCA TTARATACAC	1000
MSRV pol	TAATTAGGGA AACTCAGAAA GCCAGTACCT ATTTAGTAAG ATGGACAGCT	1050
cons ADN 41,42,43	GAATTAAGGA AACTCAAAAA GCCAATACCC ATTTAGTAAG ATGGACAACT	408
Consensus	KAATTARGGA AACTCARAAA GCCARTACCY ATTTAGTAAG ATGGACARCT	1050
MSRV pol	--A-CAGAAG TGGCTTTCCA GGCCCTAAAG AAGGCCCTAA CCCAAGCCCC	1097
cons ADN 41,42,43	GAAGCAGAAG TGGCTTTCCA GGCCCTAAAG ---------- ----------	438
Consensus	GAAGCAGAAG TGGCTTTCCA GGCCCTAAAG AAGGCCCTAA CCCAAGCCCC	1100
MSRV pol	AGTGTTCAGC TTGCCAACAG GGCAAGATTT TTCTTTATAT GCCACAGAAA	1147
cons ADN 41,42,43	---------- ---------- ---------- ---------- ----------	438
Consensus	AGTGTTCAGC TTGCCAACAG GGCAAGATTT TTCTTTATAT GCCACAGAAA	1150
MSRV pol	AAACAGGAAT AGCTCTAGGA GTCCTTACGC AGGTCTCAGG GATGAGCTTG	1197
cons ADN 41,42,43	---------- ---------- ---------- ---------- ----------	438
Consensus	AAACAGGAAT AGCTCTAGGA GTCCTTACGC AGGTCTCAGG GATGAGCTTG	1200
MSRV pol	CAACCCGTGG TATACCTGAG TAAGGAAATT GATGTAGTGG CAAAGGGTTG	1247
cons ADN 41,42,43	---------- ---------- ---------- ---------- ----------	438
Consensus	CAACCCGTGG TATACCTGAG TAAGGAAATT GATGTAGTGG CAAAGGGTTG	1250
MSRV pol	GCCTCATTGT TTATGGGTAA TGGCGGCAGT AGCAGTCTTA GTATCTGAAG	1297
cons ADN 41,42,43	---------- ---------- ---------- ---------- ----------	438
Consensus	GCCTCATTGT TTATGGGTAA TGGCGGCAGT AGCAGTCTTA GTATCTGAAG	1300
MSRV pol	CAGTTAAAAT AATACAGGGA AGAGATCTTA CTGTGTGGAC ATCTCATGAT	1347
cons ADN 41,42,43	---------- ---------- ---------- ---------- ----------	438
Consensus	CAGTTAAAAT AATACAGGGA AGAGATCTTA CTGTGTGGAC ATCTCATGAT	1350
MSRV pol	GTGAACGGCA TACTCACTGC TAAAGGAGAC TTGTGGTTGT CAGACAACCA	1397
cons ADN 41,42,43	---------- ---------- ---------- ---------- ----------	438
Consensus	GTGAACGGCA TACTCACTGC TAAAGGAGAC TTGTGGTTGT CAGACAACCA	1400
MSRV pol	TTTACTTAAT TATCAGGCTC TATTACTTGA AGAGCCAGTG CTGAGACTGC	1447
cons ADN 41,42,43	---------- ---------- ---------- ---------- ----------	438
Consensus	TTTACTTAAT TATCAGGCTC TATTACTTGA AGAGCCAGTG CTGAGACTGC	1450
MSRV pol	GCACTTGTGC AACTCTTAAA CCCGCCACAT TTCTTCCAGA CAATGAAGAA	1497
cons ADN 41,42,43	---------- ---------- ---------- ---------- ----------	438
Consensus	GCACTTGTGC AACTCTTAAA CCCGCCACAT TTCTTCCAGA CAATGAAGAA	1500
MSRV pol	AAGATAGAAC ATAACTGTCA ACAAGTAATT GCTCAAACCT ATGCTGCTCG	1547
cons ADN 41,42,43	---------- ---------- ---------- ---------- ----------	438
Consensus	AAGATAGAAC ATAACTGTCA ACAAGTAATT GCTCAAACCT ATGCTGCTCG	1550
MSRV pol	AGGGGACCTT CTAGAGGTTC CCTTGACTGA TCCCGACCTC AACTTGTATA	1597
cons ADN 41,42,43	---------- ---------- ---------- ---------- ----------	438
Consensus	AGGGGACCTT CTAGAGGTTC CCTTGACTGA TCCCGACCTC AACTTGTATA	1600

FIG 52 B

```
Trans of MSRV pol     IMPESPTPLL GRDILAKAGA IIHLNIGKGI PICCPLLEEG INPEVWAIEG     50
cons prot 41,42,43    ---------- ---------- ---------- ---------- ----------
Consensus             .......... .......... .......... .......... ..........     50

Trans of MSRV pol     QYGQAKNARP VQVKLKDSAS FPYQRKYPLR PEALQGXQKI VKDLKAQGLV    100
cons prot 41,42,43    ---------- ---------- ---------- ---------- ----------
Consensus             .......... .......... .......... .......... ..........    100

Trans of MSRV pol     KPCSSPCNTP ILGVRKPNGQ WRLVQDLRII NEAVFPLYPA VSSPYTLLSL    150
cons prot 41,42,43    ---------- ---------- ---------- ---------- ----------
Consensus             .......... .......... .......... .......... ..........    150

Trans of MSRV pol     IPEEAEWFTV LDLKDAFFCI PVRPDSQFLF AFEDPLNPTS QLTWTVLPQG    200
cons prot 41,42,43    ---------- ---------- ---------- ---------- ----------
Consensus             .......... .......... .......... .......... ..........    200

Trans of MSRV pol     FRDSPHLFGQ ALAQDLSQHS YLDTLVLQYV DDLLIVARSE TLCHQATQHL    250
cons prot 41,42,43    ---------- ----DLSQSS YLDTLVLRYM DDLLIATHSE TLCHQATQAL     36
Consensus             .......... ....DLSQ.S YLDTLVL.Y. DDLLI...SE TLCHQATQ.L    250

Trans of MSRV pol     LQFLQTCGYK VSKPKARLCS QEIRYLGLKL SKGTRALSEE RIQPILAYPH    300
cons prot 41,42,43    LNFLATCGYK VSKPKAQLCS QQVKYLGLKL SKGTRILSEE RIQPILGYPH     86
Consensus             L.FL.TCGYK VSKPKA.LCS Q...YLGLKL SKGTR.LSEE RIQPIL.YPH    300

Trans of MSRV pol     PKTLKQLRGF LGITGFCRKQ IPRYTPIARP LMILIRETQK ANTMLVRWTP    350
cons prot 41,42,43    PKTLKQLTAF LGITGFCQIW IPRYSKIARP LNIRIKETQK ANTHLVRWTP    136
Consensus             PKTLKQL..F LGITGFC... IPRY..IARP L.I.I.ETQK ANT.LVRWTP    350

Trans of MSRV pol     TEVAFQALKK ALTQAPVFSL PTGQDFSLYA TEKTGIALGV LTQVSGMSLQ    400
cons prot 41,42,43    ---------- ---------- ---------- ---------- ----------    136
Consensus             .......... .......... .......... .......... ..........    400

Trans of MSRV pol     PVVYLSKEID VVAKGWPHCL WVMAAVAVLV SEAVKIIQGR DLTVWTSHDV    450
cons prot 41,42,43    -------EAE V--------- ---------- ---------- ----------    140
Consensus             .......E.. V......... .......... .......... ..........    450

Trans of MSRV pol     NGILTAKGDL WLSDNHLLNY QALLLEEPVL RLRTCATLKP ATFLPDNEEK    500
cons prot 41,42,43    ---------- --------AF QALK------ ---------- ----------    146
Consensus             .......... .......... QAL....... .......... ..........    500

Trans of MSRV pol     IEHNCQQVIA QTYAARGDLL EVPLTDPDLN LYTDGSSLAE KGLRKAGYAV    550
cons prot 41,42,43    ---------- ---------- ---------- ---------- ----------    146
Consensus             .......... .......... .......... .......... ..........    550

Trans of MSRV pol     ISDNGILESN RLTPGTSAHL AELIALTWAL ELGEGKRVNI YSDSKYAYLV    600
cons prot 41,42,43    ---------- ---------- ---------- ---------- ----------    146
Consensus             .......... .......... .......... .......... ..........    600

Trans of MSRV pol     LHAHAAIWRE REFLTSEGTP INHQEAIRRL LLAVQKPKEV AVLHCQGHQE    650
cons prot 41,42,43    ---------- ---------- ---------- ---------- ----------    146
Consensus             .......... .......... .......... .......... ..........    650

Trans of MSRV pol     EEERETEGNR QADIEAKKAA RQDSPLEMLI EGP                      683
cons prot 41,42,43    ---------- ---------- ---------- ---                      146
Consensus             .......... .......... .......... ...                      683
```

FIG 53 A

```
cons ADN 41,42,43   GACTTGAGCC AGTCATCATA CCTGGACAAT CTTGTCCATC GGTACATGGA    50
cons ADN 1,5,8      GACTTGAGCC AGTCCTCATA CCTGGACATT CTTGTTCCTC AGTATRGGGA    50
Consensus           GACTTGAGCC AGTCMTCATA CCTGGACAWT CTTGTYCMTC RGTAYRKGGA    50

cons ADN 41,42,43   TGAGTTAGTT GTAGCCACCC ATTCAGAAAC CTTGTGCCAT CAAGCCACCC   100
cons ADN 1,5,8      TGAATTAATT ATAGCCACCC ATTCAGAAAC CTTGTGGCAY CAAGCCACCC   100
Consensus           TGARTTARTT RTAGCCACCC ATTCAGAAAC CTTGTGSCAY CAAGCCACCC   100

cons ADN 41,42,43   AAGCACTCTT AAATTTCCTT GCTACCTGTG GCTACAAGGT TTCCAAACCA   150
cons ADN 1,5,8      AAGYGCTCTT AAATTTCCTY GCTACCTGTG GC-------- -TCCAAACMA   141
Consensus           AAGYRCTCTT AAATTTCCTY GCTACCTGTG GCTACAAGGT TTCCAAACMA   150

cons ADN 41,42,43   AAGGCTCAGC TCTGCTCACA GCAGGTTAAA TACTTAGGGC TAAAATTATC   200
cons ADN 1,5,8      ARGGCTCAAC TCTGCTCACA SCAGGTTAAA TACTTAGGGC TAAAATTATC   191
Consensus           ARGGCTCARC TCTGCTCACA SCAGGTTAAA TACTTAGGGC TAAAATTATC   200

cons ADN 41,42,43   CAAAGGCACC AGAACCCTCA GTGAGGAACG TATCCAGCCT ATACTGGCTT   250
cons ADN 1,5,8      CAAAGTCRCC AGGGCCCTCA GRGAGGAACG TATCCAGCGT ATACTGGMTT   241
Consensus           CAAAGKCRCC AGRRCCCTCA GWGAGGAACG TATCCAGCST ATACTGGMTT   250

cons ADN 41,42,43   ATCCTCATCC CAAAACCCTA AAGCAACTAA CAGCGTTCCT TGGCATAACA   300
cons ADN 1,5,8      ATCCMCATCC CAWAACCMTA AAGCAACTAA GARGGTTCCT TGGCATAWCA   291
Consensus           ATCCMCATCC CAWAACCMTA AAGCAACTAA SARSGTTCCT TGGCATAWCA   300

cons ADN 41,42,43   GGTTTCTGCC AAATATGGAT TCCCAGGTAC AGCAARRTAG CCAGACCATT   350
cons ADN 1,5,8      GCCTTCTGCC GAATATGGAT TCCCVGRTAC AGYGAAATAG CCAGGCCATT   341
Consensus           GSYTTCTGCC RAATATGGAT TCCCVGRTAC AGYRARRTAG CCAGRCCATT   350

cons ADN 41,42,43   AAATACACGA ATTAAGGAAA CTCAAAAAGC CAATACCCAT TTAGTAAGAT   400
cons ADN 1,5,8      ATGTACATTA DYTAAGGAAA CTCAGAAAGC CAATACCCAT ATAGTAAGAT   391
Consensus           AWRTACAYRA DYTAAGGAAA CTCARAAAGC CARTACCCAT WTAGTAAGAT   400

cons ADN 41,42,43   GGACAACTGA AGCAGAAGTG GCTTTCCAGG CCCTAAAG                438
cons ADN 1,5,8      GGACACCTGA RACAGAAGTG GCTTTCCAGG CCCTAAAG                429
Consensus           GGACAMCTGA RRCAGAAGTG GCTTTCCAGG CCCTAAAG                438
```

FIG 53 B

```
cons prot 41,42,43  DLSQSSYLDT LVLRYMDDLL LATHSETLCH QATQALLNFL ATCGMKVSKP    50
cons prot 1,5,8     DLSQSSYLDI LVLQYGDDLI IATHSETLWH QATQALLNFL ATCGSK---Q    47
Consensus           DLSQSSYLD. LVL.Y.DDL. .ATHSETL.H QATQALLNFL ATCG.K....    50

cons prot 41,42,43  KAQLCSQQVK YLGLKLSKGT RILSEERIQP ILGYPHPKTL KQLTAFLGIT   100
cons prot 1,5,8     KAQLCSQQVK YLGLKLSKVT RALREERIQR ILAYPHPKTL KQLRGFLGIT    97
Consensus           KAQLCSQQVK YLGLKLSK.T R.L.EERIQ. IL.YPHPKTL KQL..FLGIT   100

cons prot 41,42,43  GFCQIWIPRY SKIARPLNTR IKETQKANTH LVRWTPEAEV AFQALK       146
cons prot 1,5,8     AFCRIWIPRY SEIARPLQTL XKETQKANTH IVRWTPEIEV AFQALK       143
Consensus           .FC.IWIPRY S.IARPL.T. .KETQKANTH .VRWTPE.EV AFQALK       146
```

INTERNATIONAL SEARCH REPORT

Inter   nal Application No
PCT/IB 97/01482

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/48 C12N5/08 C12N7/02 C07K14/15 C12N9/12
C12N9/22 C12Q1/70 C07K16/10 G01N33/569 A61K39/21
A61K39/42 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12Q C07K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 731 168 A (BIO MERIEUX) 11 September 1996 see the whole document ---	1-35
A	WO 95 21256 A (BIO MERIEUX ;PERRON HERVE (FR); MALLET FRANCOIS (FR); MANDRAND BER) 10 August 1995 see the whole document ---	1-35
A	WO 94 28138 A (UNIV LONDON ;GARSON JEREMY (GB); TUKE PHILIP (GB)) 8 December 1994 see the whole document --- -/--	1-35

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
22 April 1998	08/05/1998
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